As filed with the United States Securities and Exchange Commission on October 23, 2018.

Registration Statement No. 333-227698

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Amendment No. 1
to
Form F-1

REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Orchard Rx Limited[1]

(Exact name of registrant as specified in its charter)

England and Wales	2836	Not applicable
(State or other jurisdiction of incorporation or organization)	(Primary Standard Industrial Classification Code Number)	(I.R.S. Employer Identification Number)

108 Cannon Street
London EC4N 6EU
United Kingdom
Tel: +44 (0) 203 384 6700

(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Cogency Global Inc.
10 East 40th Street 10th Floor
New York, New York 10016
+1 212 947 7200

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

Mitchell S. Bloom Michael H. Bison Goodwin Procter LLP 100 Northern Avenue Boston, MA 02210 (617) 570-1000	Andrew Harrow Goodwin Procter (UK) LLP 100 Cheapside London EC2V 6DY United Kingdom +44 20 7447 4200	Deanna L. Kirkpatrick Marcel R. Fausten Davis Polk & Wardwell LLP 450 Lexington Avenue New York, NY 10017 (212) 450-4000

Approximate date of commencement of proposed sale to public: As soon as practicable after this registration statement becomes effective.

If any of the securities being registered on this form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, check the following box. ☐

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(d) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act.

Emerging growth company ☑

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards† provided pursuant to Section 7(a)(2)(B) of the Securities Act. ☐

† The term "new or revised financial accounting standards" refers to any update issued by the Financial Accounting Standards Board to its Accounting Standards Codification after April 5, 2012.

CALCULATION OF REGISTRATION FEE

TITLE OF EACH CLASS OF SECURITIES BEING REGISTERED	AMOUNT TO BE REGISTERED(1)(2)	PROPOSED MAXIMUM OFFERING PRICE PER SHARE	PROPOSED MAXIMUM AGGREGATE OFFERING PRICE(1)(2)	AMOUNT OF REGISTRATION FEE(3)
Ordinary shares, nominal value £0.10 per share(4)	15,333,332	$16.00	$245,333,312	$29,735

(1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(a) under the Securities Act of 1933, as amended.

(2) Includes shares represented by American Depositary Shares, or ADSs, that are issuable upon exercise of the underwriters' option to purchase additional shares.

(3) Calculated pursuant to Rule 457(a) under the Securities Act of 1933, as amended, based on an estimate of the proposed maximum aggregate offering price. Of this amount, a total of $20,907 was previously paid.

(4) These ordinary shares are represented by ADSs, each of which represents one ordinary share of the registrant. ADSs issuable upon deposit of the ordinary shares registered hereby are being registered pursuant to a separate registration statement on Form F-6 (File No. 333-227905).

The registrant hereby amends this registration statement on such date or dates as may be necessary to delay its effective date until the registrant shall file a further amendment which specifically states that this registration statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933, as amended, or until the registration statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), shall determine.

1. We intend to alter the legal status of our company under English law from a private limited company by re-registering as a public limited company and changing our name from Orchard Rx Limited to Orchard Therapeutics plc prior to the completion of this offering. Prior to re-registration, Orchard Therapeutics Limited will change its name to Orchard Therapeutics (Europe) Limited.

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The information contained in this preliminary prospectus is not complete and may be changed. We may not sell these securities until the registration statement filed with the Securities and Exchange Commission is effective. This preliminary prospectus is not an offer to sell these securities and we are not soliciting offers to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to completion, dated October 23, 2018

Preliminary prospectus

American depositary shares
Representing 13,333,333 ordinary shares

Orchard therapeutics

We are offering 13,333,333 American Depositary Shares, or ADSs. Each ADS represents one ordinary share. The ADSs may be evidenced by American Depositary Receipts, or ADRs. This is our initial public offering of our ADSs and no public market currently exists for our ADSs or ordinary shares.

We expect the initial public offering price is expected to be between $14.00 and $16.00 per ADS. We intend to apply to list our ADSs on The Nasdaq Global Market under the symbol "ORTX."

Investing in our ADSs involves a high degree of risk. Before buying any ADSs, you should carefully read the discussion of material risks of investing in our ADSs in "Risk factors" beginning on page 14 of this prospectus.

We are an "emerging growth company" as defined under the federal securities laws and, as such, will be subject to reduced public company reporting requirements. See "Prospectus summary—Implications of being an emerging growth company and a foreign private issuer" for additional information.

Neither the U.S. Securities and Exchange Commission nor any other regulatory body has approved or disapproved of these securities or passed upon the accuracy or adequacy of this prospectus. Any representation to the contrary is a criminal offense.

	Per ADS	Total
Public offering price	$	$
Underwriting discounts and commissions(1)	$	$
Proceeds to Orchard Therapeutics, before expenses	$	$

(1) See "Underwriting" for additional information regarding underwriting compensation

Delivery of the ADSs is expected to be made on or about , 2018. We have granted the underwriters an option for a period of 30 days to purchase an additional 1,999,999 ADSs. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $ million, and the total proceeds available to us, before expenses, will be $ million, assuming a midpoint of the range.

At our request, the underwriters have reserved up to 666,666 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the initial public offering price per ADS through a directed share program to directors, officers, employees and certain other individuals associated with us. See "Underwriting."

J.P. Morgan **Goldman Sachs & Co. LLC** **Cowen**

Wedbush PacGrow

Prospectus dated , 2018

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We are responsible for the information contained in this prospectus and any free writing prospectus we prepare or authorize. We have not, and the underwriters have not, authorized anyone to provide you with different information, and we and the underwriters take no responsibility for any other information others may give you. We are not, and the underwriters are not, making an offer to sell our ADSs in any jurisdiction where the offer or sale is not permitted. You should not assume that the information contained in this prospectus is accurate as of any date other than the date on the front cover of this prospectus, regardless of the time of delivery of this prospectus or the sale of any ADSs.

For investors outside the United States: Neither we nor the underwriters have done anything that would permit this offering or possession or distribution of this prospectus in any jurisdiction, other than the United States, where action for that purpose is required. Persons outside the United States who come into possession of this prospectus must inform themselves about, and observe any restrictions relating to, the offering of the ADSs and the distribution of this prospectus outside the United States.

We are incorporated under the laws of England and Wales. Under the rules of the U.S. Securities and Exchange Commission, or the SEC, we are currently eligible for treatment as a “foreign private issuer.” As a foreign private issuer, we will not be required to file periodic reports and financial statements with the SEC as frequently or as promptly as domestic registrants whose securities are registered under the Securities Exchange Act of 1934, as amended, or the Exchange Act.

Market, industry and other data

This prospectus contains estimates, projections and other information concerning our industry, our business, and the markets for our product candidates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties, and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from our own internal estimates and research as well as from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

In addition, assumptions and estimates of our and our industry's future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in the section titled "Risk factors." These and other factors could cause our future performance to differ materially from our assumptions and estimates. See "Special note regarding forward-looking statements."

About this prospectus

Prior to the completion of this offering, we will undertake a corporate reorganization described under the section titled “Corporate reorganization,” pursuant to which Orchard Therapeutics Limited will become a wholly owned subsidiary of Orchard Rx Limited, a recently formed holding company with nominal assets and no liabilities, contingencies, or commitments, which will not have conducted any operations prior to this offering other than acquiring the entire issued share capital of Orchard Therapeutics Limited. Prior to the completion of this offering, we intend to re-register Orchard Rx Limited as a public limited company and to change our name from Orchard Rx Limited to Orchard Therapeutics plc. Prior to the re-registration of Orchard Rx Limited as a public limited company, Orchard Therapeutics Limited will change its name to Orchard Therapeutics (Europe) Limited.

Unless otherwise indicated or the context otherwise requires, all references in this prospectus to the terms “Orchard Therapeutics Limited,” “Orchard Rx Limited,” “Orchard Therapeutics plc,” “the company,” “we,” “us” and “our” refer to (i) Orchard Therapeutics Limited and its wholly owned U.S. subsidiary prior to the completion of our corporate reorganization, (ii) Orchard Rx Limited and its subsidiaries after the completion of our corporate reorganization and (iii) Orchard Therapeutics plc and its subsidiaries after the re-registration of Orchard Rx Limited as a public limited company, which is expected to occur prior to the completion of this offering. See “Corporate reorganization” for more information.

We own various trademark registrations and applications, and unregistered trademarks, including Orchard Therapeutics plc and our corporate logo. All other trade names, trademarks and service marks of other companies appearing in this prospectus are the property of their respective holders. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend to use or display other companies’ trademarks and trade names to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

Presentation of financial information

We maintain our books and records in pounds sterling, our results are subsequently converted to U.S. dollars and we prepare our consolidated financial statements in accordance with generally accepted accounting principles in the United States, or U.S. GAAP, as issued by the Financial Accounting Standards Board. All references in this prospectus to "$" are to U.S. dollars and all references to "£" are to pounds sterling. Unless otherwise indicated, certain pounds sterling amounts contained in this prospectus have been translated into U.S. dollars at the rate of $1.3197 to £1.00, which was the noon buying rate of the Federal Reserve Bank of New York on June 29, 2018, the last business day of the period ended June 30, 2018. These translations should not be considered representations that any such amounts have been, could have been or could be converted into pounds sterling at that or any other exchange rate as of that or any other date. See "Exchange rate information" for more information.

We have made rounding adjustments to some of the figures included in this prospectus. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them. We have historically conducted our business through Orchard Therapeutics Limited and our U.S. subsidiary, and therefore our historical consolidated financial statements present the consolidated results of operations of Orchard Therapeutics Limited. Following the completion of this offering, and after the consummation of the transactions described under the section titled "Corporate reorganization," our consolidated financial statements will present the consolidated results of operations of Orchard Therapeutics plc.

Prospectus summary

The following summary highlights information contained elsewhere in this prospectus and does not contain all of the information you should consider before investing in our ADSs. You should read the entire prospectus carefully, including "Risk factors," "Management's discussion and analysis of financial condition and results of operations," and our consolidated financial statements and the related notes, in each case included in this prospectus, before making an investment decision.

Overview

We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, hematopoietic stem cells (HSCs) into a gene-modified drug product to treat the patient's disease through a single administration. We achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process, resulting in a drug product that can then be re-introduced into the patient at the bedside.

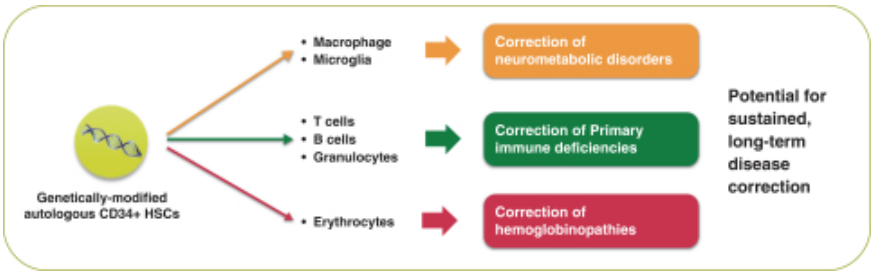
To date, our commercial product and clinical-stage product candidates have been administered in over 150 patients across five different diseases. These results, in combination with our deep expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially transformative therapies to patients suffering from a broad range of rare diseases.

We are initially focusing our autologous *ex vivo* gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Our portfolio currently includes Strimvelis, our commercial-stage gammaretroviral-based product for the treatment of adenosine deaminase-severe combined immunodeficiency, or ADA-SCID, five lentiviral product candidates in clinical-stage development and several other product candidates in preclinical development. We anticipate making near-term regulatory submissions for approval of three of our most advanced clinical-stage product candidates. These include OTL-101 for the treatment of ADA-SCID, OTL-200 for the treatment of metachromatic leukodystrophy, or MLD, and OTL-103 for the treatment of Wiskott-Aldrich syndrome, or WAS.

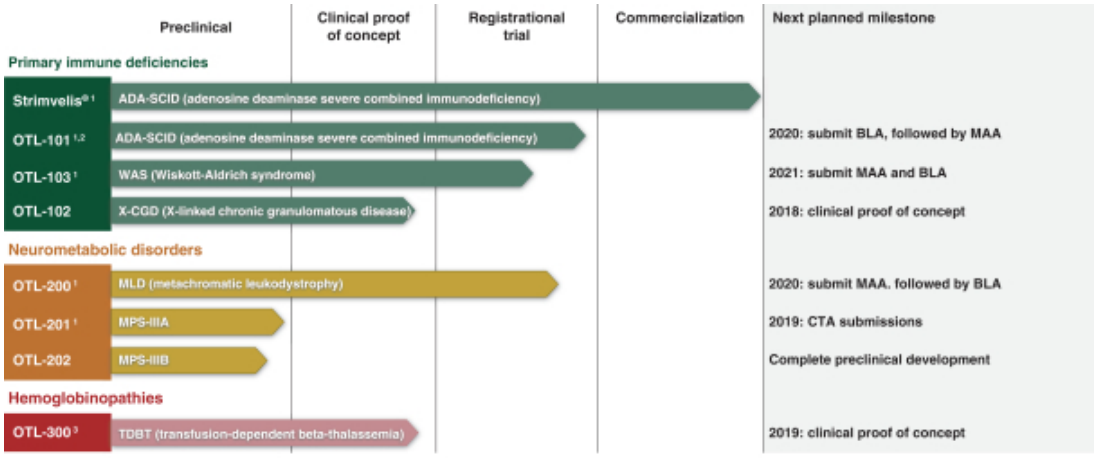
We intend to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. The indications we are initially targeting in our primary immune deficiencies and neurometabolic franchises (ADA-SCID, MLD, WAS, X-CGD, and MPS-IIIA) alone have a combined annual incidence rate of between 1,000 and 2,000 patients in markets around the world where treatments for rare diseases are often reimbursed. Based on this, we believe the total addressable market potential in the diseases areas underlying our five lead programs could be greater than $2 billion annually. In addition, certain indications such as X-CGD and WAS have large existing populations with pre-existing disease that could be eligible for our treatments upon receiving marketing approval, which could increase the size of our market opportunity further.

We believe our approach of using lentiviral vectors to genetically modify HSCs has wide-ranging applicability to a large number of indications. The ability of HSCs to differentiate into multiple cell types allows us to deliver gene-modified cells to multiple physiological systems, including the

central nervous system, immune system and red blood cell lineage, thereby potentially enabling the correction of a wide range of diseases. By leveraging the innate self-renewing capability of HSCs as well as the ability of lentiviral vectors to achieve stable integration of a modified gene into the chromosomes of HSCs, our gene therapies have the potential to provide a durable effect following a single administration.



We have a broad and advanced portfolio of wholly-owned commercial and development stage products and product candidates. In April 2018, we strengthened our portfolio with our acquisition of Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT from Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD, or, together, GSK.



1: Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher (U.S.)
2: Breakthrough Therapy Designation
3: Priority Medicines (PRIME) Designation

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare or ultra-rare indications, we believe our clinical programs will generally be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. For purposes of this prospectus, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial.

We currently anticipate making submissions for regulatory approval of each of our three lead product candidates within the next three years. For each of these lead product candidates, we

are in ongoing discussions with the applicable regulatory authorities with respect to the clinical and other data required for regulatory submission.

The timelines described above reflect our current expectations and beliefs based on our regulatory interactions to date. However, we do not yet have definitive feedback from these regulatory agencies on the scope or adequacy of the requisite data necessary to support an approval. Notably, we expect to have additional chemistry, manufacturing and control, or CMC, focused meetings with these regulatory agencies prior to any submission for marketing approval to obtain their concurrence on the robustness of analytical comparability data between academic and commercial manufacturing processes, vector and drug product process characterization and process validation approach, including demonstration of manufacturing state of control. We also plan to discuss the data required for the inclusion of patients' mobilized peripheral blood as the cellular source material, together with patient bone marrow, in the label for our product candidates for which we obtain approval. Pending the outcome of these discussions, we may elect to initially seek approval of our product candidates using one cellular source material and subsequently seek approval for the use of the other cellular source material. As a result of these ongoing discussions, additional preclinical and/or clinical data may be required to support an approval, in which case we may experience delays in our regulatory timelines.

Our three lead product development programs are summarized below:

- OTL-101 is our product candidate for ADA-SCID, a rare, life-threatening inherited disease of the immune system. OTL-101 has received orphan drug designation from the FDA and the EMA for treatment of ADA-SCID, and Breakthrough Therapy Designation from the FDA. We plan to submit a BLA for OTL-101 with the FDA in 2020, followed by an MAA with the EMA. Based on our ongoing discussions with the FDA, we expect our BLA submission will include data from our registrational trial at UCLA of 20 patients treated with a fresh product formulation, supportive data derived from at least five patients treated with a cryopreserved formulation at UCLA and additional data derived from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, as well as any other patients with adequate follow-up at the time of submission. See "Business—Our Pipeline—Gene therapy for the treatment of ADA-SCID—Regulatory Pathway for OTL-101." In the European Union, our commercial program, Strimvelis, has been available since 2016 as the only approved gene therapy option for patients with ADA-SCID. The EMA approved Strimvelis for treatment of children with ADA-SCID with no suitable HLA-matched stem cell donor.
- OTL-200 is our product candidate for MLD, a rare and rapidly progressive neurometabolic disorder. OTL-200 has received orphan drug designation from the FDA and the EMA for the treatment of MLD. We plan to submit an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA. Based on our ongoing discussions with EMA, we expect our MAA submission will include clinical data from a registrational trial of 20 late infantile and early juvenile MLD patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as any other patients with adequate follow-up at the time of submission. See "Business—Our Pipeline—Gene therapy for treatment of MLD—Regulatory Pathway for OTL-200." There are no approved therapies for treatment of MLD available today.

- OTL-103 is our product candidate for WAS, a rare, life-threatening inherited disease affecting the patient's immune system and platelets. OTL-103 has received orphan drug designation from the FDA and the EMA for the treatment of WAS. We plan to submit an MAA with the EMA and a BLA with the FDA for OTL-103 in 2021. Based on our ongoing discussions with EMA and FDA, we expect that our MAA and BLA submissions will include clinical data from a registrational trial of 8 patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as additional patients with adequate follow-up at the time of submission, treated with a fresh product formulation under compassionate use. See "Business—Our Pipeline—Gene therapy for treatment of WAS—Regulatory Pathway for OTL-103."

Beyond these three lead product candidates, we are evaluating our other clinical-stage product candidates OTL-102 for X-CGD and OTL-300 for transfusion-dependent beta-thalassemia, or TDBT, in clinical trials for which enrollment and/or follow-up are ongoing. We are also expanding our neurometabolic disorders franchise with the development of two preclinical programs, OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and OTL-202 for mucopolysaccharidosis type IIIB, or MPS-IIIB. We anticipate submitting a clinical trial application, or CTA, with the applicable regulatory authority in Europe for MPS-IIIA by the end of 2019 and to continue to progress preclinical development of MPS-IIIB.

The table below reflects the total number of patients treated, the maximum follow-up, and the range of patient follow-up as of September 2018, as well as the average age of death without treatment, across the lead programs in our franchise areas.

Franchise	Program	Patients treated with gene therapy[1]	Follow-up post gene therapy (minimum)	Follow-up post gene therapy (maximum)[2]
Primary immune deficiencies	**OTL-101** (ADA-SCID)	61	0.2 years	6.5 years
	Strimvelis® (ADA-SCID)	24	0.2 years	18.0 years
	OTL-103 (WAS)	16	0.0 years	8.2 years
	OTL-102 (X-CGD)	10	1.1 years	2.8 years
Neurometabolic disorders	**OTL-200** (MLD)	31	0.0 years	8.3 years
Hemoglobinopathies	**OTL-300** (TDBT)	9	0.8 years	3.0 years
Total		151		

(1) The number of patients reflects all patients treated in the development phase, including in clinical trials and compassionate use. We refer to patients treated through a compassionate use, early access or hospital exemption or special license program as compassionate use patients.

(2) Published literature in our franchise areas indicate that, left untreated, each of our lead target indications carries significant risk of mortality: (i) ADA-SCID patients have a mortality rate of 14% at one year of age and 33% at two years of age; (ii) late infantile MLD patients and juvenile MLD patients have mortality rates of 50% and 44% at five years of age and 10 years of age, respectively, (iii) WAS patients have a mortality rate of 62% at 15 years of age, (iv) X-CGD patients have a mortality rate of 40% at 35 years of age, and (v) left untreated, mortality in TDBT patients generally occurs within the first three years of life. We believe follow-up data across our five clinical-stage programs support the transformative nature of our approach in indications that are almost always fatal in early life without treatment.

The diseases we are targeting affect patients around the world, requiring an infrastructure to deliver gene therapies globally. We are therefore building a commercial-scale manufacturing infrastructure and leveraging technologies that will allow us to deliver our gene therapies

globally in a fully-integrated manner. In order to meet anticipated demand for our growing pipeline of product candidates and planned product offerings, we are initially utilizing our existing network of contract manufacturing organizations, or CMOs, to manufacture vectors and drug product. In addition, we currently operate two development laboratory facilities in California and plan to invest in additional facilities to accommodate our expanding technical operations and implement in-house drug product and vector manufacturing capabilities.

Cryopreservation of our gene-modified HSCs is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide, facilitating both local treatment and local product reimbursement. In anticipation of commercialization, we have developed cryopreserved formulations of our three most advanced product candidates and are working to demonstrate comparability to the fresh cell formulations used in our registrational trials. We are also establishing cryopreserved product formulations for all of our earlier stage product candidates.

We have global commercial rights to Strimvelis and all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe, subject to obtaining necessary marketing approvals in those jurisdictions. We plan to deploy a focused commercial infrastructure to deliver our product candidates to patients, and are focused on working closely with all relevant stakeholders, including patients, caregivers, specialist physicians and payors, to ensure the widest possible post-approval access for our product candidates.

As we continue to develop and expand our portfolio, we believe that the deep experience of our management team and our extensive academic relationships are key strategic strengths. Our management team has over 100 years of collective experience in rare diseases and in the manufacturing, preclinical and clinical development and commercialization of gene and cell therapies. In addition, we partner with leading academic institutions, which are pioneers in autologous *ex vivo* gene therapy. We plan to leverage our internal expertise combined with our relationships with leading academic institutions to transition our lead clinical-stage product candidates to commercialization and continue to expand our portfolio of autologous *ex vivo* gene therapy products for rare diseases.

Corporate information

Orchard Rx Limited was originally incorporated under the laws of England and Wales in August 2018 to become a holding company for Orchard Therapeutics Limited. Orchard Therapeutics Limited was originally incorporated under the laws of England and Wales in September 2015 as Newincco 1387 Limited and subsequently changed its name to Orchard Therapeutics Limited in November 2015. Our registered office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom, and our telephone number is +44 (0) 203 384 6700. Our website address is www.orchard-tx.com. We do not incorporate the information on or accessible through our website into this prospectus, and you should not consider any information on, or that can be accessed through, our website as part of this prospectus.

Corporate reorganization

Pursuant to the terms of a corporate reorganization that will be completed prior to the closing of this offering, all of the interests in Orchard Therapeutics Limited were exchanged for the same number and class of newly issued shares of Orchard Rx Limited and, as a result, Orchard

Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited. Prior to the consummation of this offering, Orchard Rx Limited will re-register as a public limited company and change its name to Orchard Therapeutics plc and Orchard Therapeutics Limited will change its name to Orchard Therapeutics (Europe) Limited. Please see “Corporate reorganization” for more information.

Recent financing

In August 2018, we completed an approximately $150.0 million private placement through the issuance of Series C convertible preferred shares led by Deerfield Management and with participation from 18 other dedicated healthcare funds.

Risks associated with our business

Our business is subject to a number of risks of which you should be aware before making an investment decision. You should carefully consider all of the information set forth in this prospectus and, in particular, should evaluate the specific factors set forth in the section titled “Risk factors” before deciding whether to invest in our ADSs. Among these important risks are, but not limited to, the following:

- We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.
- The interim data and ad hoc analyses summarized in this prospectus are current as of the dates specified and are preliminary in nature. Our company-sponsored clinical trials of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and the investigator-sponsored clinical trials for OTL-102 for X-CGD and OTL-300 for TDBT are ongoing and not complete. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.
- The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing approval, the FDA and/or the EMA may require us to conduct additional clinical trials, or evaluate patients for an additional follow-up period.
- Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business.
- We currently have limited sales and marketing capabilities. If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates that may be approved, we may not be successful in commercializing our product candidates if and when approved, and we may be unable to generate any product revenue.
- Third parties may claim that we are infringing, misappropriating or otherwise violating their intellectual property rights, which intellectual property infringement may prevent or delay our development and commercialization efforts and have a material adverse effect on our business.

- We are aware of third-party issued U.S. and foreign patents relating to the lentiviral vectors used in the manufacture or use of our product candidates. While we believe that we have defenses against a claim of infringement of these patents, including that such patents would not be infringed by one or more of our product candidates and/or are not valid, we cannot guarantee that a court of competent jurisdiction will agree with our assessment.
- We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.

Implications of being an emerging growth company and a foreign private issuer

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. An emerging growth company may take advantage of specified reduced reporting and other burdens that are otherwise applicable generally to public companies. These provisions include:

- a requirement to have only two years of audited financial statements in addition to any required interim financial statements and correspondingly reduced Management's Discussion and Analysis of Financial Condition and Results of Operations disclosure; and
- an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act of 2002 or the Sarbanes-Oxley Act. See "Management's discussion and analysis of financial condition and results of operations—emerging growth company status."

We may take advantage of these exemptions for up to five years or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company upon the earlier to occur of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; (iii) the date on which we are deemed to be a large accelerated filer under the rules of the SEC; or (iv) the last day of the fiscal year following the fifth anniversary of this offering. We may choose to take advantage of some but not all of these exemptions.

In addition, under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards until such time as those standards apply to private companies.

We are also considered a "foreign private issuer." Even after we no longer qualify as an emerging growth company, as long as we qualify as a foreign private issuer under the Exchange Act, we will be exempt from certain provisions of the Exchange Act that are applicable to U.S. domestic public companies, including:

- the sections of the Exchange Act regulating the solicitation of proxies, consents or authorizations with respect to a security registered under the Exchange Act;
- the requirement to comply with Regulation FD, which requires selective disclosure of material information;

- the sections of the Exchange Act requiring insiders to file public reports of their share ownership and trading activities and liability for insiders who profit from trades made in a short period of time; and
- the rules under the Exchange Act requiring the filing with the SEC of quarterly reports on Form 10-Q containing unaudited financial and other specified information, or current reports on Form 8-K upon the occurrence of specified significant events.

Both foreign private issuers and emerging growth companies are also exempt from certain more stringent executive compensation disclosure rules. Thus, even if we no longer qualify as an emerging growth company, but remain a foreign private issuer, we will continue to be exempt from the more stringent compensation disclosures required of companies that are neither an emerging growth company nor a foreign private issuer. As a result, we do not know if some investors will find our ADSs less attractive, which may result in a less active trading market for our ADSs or more volatility in the price of our ADSs.

The offering

ADSs offered by us	13,333,333 ADSs, each representing one ordinary share.
Underwriters' option to purchase additional ADSs	We have granted the underwriters an option for a period of 30 days from the date of this prospectus to purchase up to an additional 1,999,999 ADSs from us.
Ordinary shares to be outstanding immediately after this offering	83,094,818 ordinary shares (or 85,094,817 ordinary shares if the underwriters exercise in full their option to purchase an additional 1,999,999 ADSs).
American depositary shares	Each ADS represents one ordinary share, nominal value £0.10 per share. You will have the rights of an ADS holder or beneficial owner (as applicable) as provided in the deposit agreement among us, the depositary and holders and beneficial owners of ADSs from time to time. To better understand the terms of our ADSs, see "Description of American depositary shares." We also encourage you to read the deposit agreement, the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part.
ADS depositary	Citibank, N.A.
Use of proceeds	We estimate that the net proceeds to us from this offering, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, to be approximately $181.9 million based on an assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus. We intend to use the net proceeds from this offering to fund ongoing development of our product candidates; ongoing commercialization of Strimvelis in the European Union and the expansion of our marketing and sales infrastructure in key markets, including the United States and Europe; design, construction, and operation of our own manufacturing facility; and the remainder for ongoing business development, general and administrative expenses, working capital and other general corporate purposes. See "Use of proceeds" for a more complete description of the intended use of proceeds from this offering.
Directed share program	At our request, the underwriters have reserved up to 666,666 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the

	initial public offering price per ADS through a directed share program, to directors, officers, employees and certain other individuals associated with us. If purchased by these persons, these ADSs will not be subject to a lock-up restriction. The number of ADSs available for sale to the general public will be reduced by the number of reserved ADSs sold to these individuals. Any reserved ADSs not purchased by these individuals will be offered by the underwriters to the general public on the same basis as the other ADSs offered pursuant to this prospectus. See “Underwriting.”
Risk factors	See “Risk factors” and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our ADSs.
Proposed Nasdaq Global Market listing	“ORTX.”

Unless otherwise stated in this prospectus, the 83,094,818 ordinary shares to be outstanding after this offering gives effect to the corporate reorganization described under the section titled “Corporate reorganization” to be completed prior to the closing of this offering and is based on 9,592,585 of our ordinary shares outstanding as of September 30, 2018, and gives effect to the conversion of all of our outstanding convertible preferred shares into 60,168,900 ordinary shares immediately prior to the closing of this offering, and excludes:

- 10,135,454 ordinary shares issuable upon the exercise of options for ordinary shares outstanding as of September 30, 2018, with a weighted-average exercise price of $2.79 per share;
- an additional 14,191 ordinary shares reserved for issuance under our 2016 Employee Share Option Plan, or the 2016 Plan, as of September 30, 2018, which shares will no longer be reserved following this offering;
- an additional 4,254,741 ordinary shares that will be made available for future issuance under our 2018 Share Option and Incentive Plan upon the effectiveness of the registration statement of which this prospectus forms a part; and
- an additional 850,948 ordinary shares that will be made available for future issuance under our 2018 Employee Share Purchase Plan, or the ESPP, upon the effectiveness of the registration statement of which this prospectus forms a part.

Unless otherwise indicated, all information contained in this prospectus also reflects and assumes:

- the conversion of all of our outstanding convertible preferred shares into an aggregate of 60,168,900 ordinary shares upon the closing of this offering;
- no issuance or exercise of outstanding options after September 30, 2018;
- a 1-for-0.8003 reverse split of our ordinary and convertible preferred shares to be effected prior to completion of this offering; and
- no exercise by the underwriters of their option to purchase up to 1,999,999 additional shares of ADSs in this offering.

Summary consolidated financial data

The following tables present the summary consolidated financial data as of the dates and for the periods indicated for Orchard Therapeutics Limited. We derived the summary consolidated statements of operations and comprehensive loss data for the years ended December 31, 2016 and 2017 from our audited consolidated financial statements included elsewhere in this prospectus and, other than pro forma and supplemental pro forma amounts, do not reflect the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The consolidated statements of operations data for the six months ended June 30, 2017 and 2018 and the consolidated balance sheet data as of June 30, 2018 have been derived from our unaudited condensed consolidated financial statements included elsewhere in this prospectus, have been prepared on the same basis as the audited consolidated financial statements and, other than pro forma and supplemental pro forma amounts, do not reflect the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. In the opinion of management, the unaudited data reflects all adjustments, consisting only of normal recurring adjustments, necessary for a fair statement of the financial information contained in those statements. We prepare our consolidated financial statements in accordance with U.S. GAAP. Our historical unaudited condensed consolidated financial statements as of and for the six months ended June 30, 2018 have been restated. See Note 1 to the unaudited condensed consolidated financial statements included elsewhere in this prospectus.

Our historical results are not necessarily indicative of our future results. You should read this data together with our consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the sections titled “Selected consolidated financial data”, “Capitalization” and “Management’s discussion and analysis of financial condition and results of operations.”

Our functional currency is the pound sterling. However, for financial reporting purposes, our financial statements, which are prepared using the functional currency, have been translated into U.S. dollars. Our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates and shareholders’ equity is translated based on historical exchange rates. Translation adjustments are not included in determining net loss but are included in foreign exchange translation adjustment within accumulated other comprehensive (loss) income, a component of shareholders’ equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in other expense in the statement of operations and comprehensive loss.

As of June 29, 2018, the last business day of the period ended June 30, 2018, the representative exchange rate was £1.00 = $1.3197.

In August 2018, Orchard Rx Limited was incorporated under the laws of England and Wales to become the holding company for Orchard Therapeutics Limited pursuant to our corporate reorganization. See “Corporate reorganization.” Prior to this offering, Orchard Rx Limited has

only engaged in activities incidental to its formation, the corporate reorganization and this offering. Prior to the completion of this offering, we intend to re-register Orchard Rx Limited as a public limited company and change our name from Orchard Rx Limited to Orchard Therapeutics plc. Following the corporate reorganization, the historical consolidated financial statements of Orchard Therapeutics plc will be retrospectively adjusted to include the historical financial results of Orchard Therapeutics Limited for all periods presented.

	Year ended December 31,		Six months ended June 30,	
	2016	2017	2017	2018 (as restated)
	(in thousands, except share and per share data)			
Consolidated Statement of Operations and Comprehensive Loss Data:				
Operating expenses:				
Research and development	$ 16,206	$ 32,527	$ 10,546	$ 160,162
General and administrative	2,997	5,985	2,270	11,948
Total operating expenses	19,203	38,512	12,816	172,110
Loss from operations	(19,203)	(38,512)	(12,816)	(172,110)
Other income (expense), net	138	(1,179)	(400)	401
Net loss before income taxes	(19,065)	(39,691)	(13,216)	(171,709)
Income tax expense	(20)	(53)	42	165
Net loss attributable to ordinary shareholders	$ (19,085)	$ (39,744)	$ (13,174)	$ (171,544)
Other comprehensive (loss) income:				
Foreign currency translation adjustment	(271)	4,398	2,070	1,970
Total comprehensive loss	$ (19,356)	$ (35,346)	$ (11,104)	$ (169,574)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.15)	$ (3.58)	$ (1.24)	$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	8,872,333	11,086,808	10,648,967	12,615,109
Pro forma net loss per share attributable to ordinary shares, basic and diluted (unaudited)(1)	$ (2.69)	$ (4.48)	$ (1.55)	$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited) (1)	7,100,528	8,872,768	8,522,366	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shares, basic and diluted (unaudited)(2)		$ (1.24)		$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)(2)		32,056,206		49,349,711

	As of June 30, 2018		
	Actual (as restated)	Pro Forma (3)	Pro Forma As adjusted (4)
		(in thousands)	
Consolidated Balance Sheet Data:			
Cash	$ 48,762	$ 196,742	$ 378,592
Working capital(5)	15,770	163,750	345,600
Total assets	64,646	212,626	394,476
Shareholders' equity:			
Convertible preferred shares	229,709	—	—
Ordinary shares	—	1	8,680
Additional paid-in capital	9,885	387,572	560,743
Accumulated other comprehensive (loss) income	6,097	6,097	6,097
Accumulated deficit	(230,945)	(230,945)	(230,945)
Total shareholders' equity	14,746	162,725	344,575

(1) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the years ended December 31, 2016 and 2017, and for the six months ended June 30, 2017 and 2018, give effect to the 1-for-0.8003 reverse split of all ordinary shares as part of the corporate reorganization. Such pro forma data will become the historical net loss per share attributable to ordinary shares, basic and diluted, of Orchard Therapeutics plc upon consummation of the corporate reorganization.

(2) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the periods ended December 31, 2017 and June 30, 2018 give effect to (i) the automatic conversion of all outstanding convertible preferred shares, as if the conversion had occurred at the later of January 1, 2017 or the issuance dates of the preferred shares, and (ii) the 1-for-0.8003 reverse split of all ordinary and convertible preferred shares; further, the shares to be sold in the proposed offering are excluded from the unaudited pro forma basic and diluted loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the year ended December 31, 2017 and the period ended June 30, 2018. See Note 10 to our audited financial statements included in this prospectus for further details on the calculation of unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders.

(3) The pro forma balance sheet data gives effect to the sale of 13,942,474 (after giving effect to the 1-for-0.8003 reverse split) shares of Series C convertible preferred shares in August 2018 for net cash proceeds of $148.0 million, which resulted in an increase of cash and additional paid-in capital of $148.0 million. In addition, the pro forma balance sheet data gives effect to the conversion of all outstanding convertible preferred shares as of June 30, 2018 into an aggregate of 46,226,426 (after giving effect to the 1-for-0.8003 reverse split) ordinary shares upon the closing of this offering, which resulted in a reduction of convertible preferred shares of $229.7 million and an increase in additional paid-in capital of $229.7 million and $1,000 of ordinary shares.

(4) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 13,333,333 ADSs our ordinary shares in this offering at an assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us. The pro forma as adjusted balance sheet also takes into account the corporate reorganization in which the nominal value of our ordinary shares is adjusted from £0.00001 to £0.08003 per share.

The pro forma as adjusted balance sheet data discussed above is illustrative only and will change based on the actual initial public offering price and other terms of this offering determined at pricing. Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, working capital and total shareholders' equity by $12.4 million, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. An increase (decrease) of 1,000,000 in the number of ADSs offered by us, as set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, total shareholders' equity and total capitalization by $14.0 million, assuming no change in the initial public offering price per ADS.

(5) We define working capital as current assets less current liabilities.

Risk factors

Investing in our ADSs involves a high degree of risk. Before deciding whether to invest, you should carefully consider the risks described below, including our consolidated financial statements and the related notes included elsewhere in this prospectus. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or growth prospects. In such an event, the market price of our ADSs could decline and you may lose all or part of your investment.

Risks related to our financial position and need for additional capital

We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.

Since inception, we have incurred net losses. We incurred net losses of $19.1 million, $39.7 million and $171.5 million for the years ended December 31, 2016 and 2017, and the six months ended June 30, 2018, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union, building a global commercial infrastructure to support anticipated commercialization of OTL-101 for adenosine deaminase-severe combined immunodeficiency, or ADA-SCID, OTL-200 for metachromatic leukodystrophy, or MLD, and OTL-103 for Wiskott-Aldrich syndrome, or WAS, if such product candidates are approved, as well as expanding our team. To date, Strimvelis is our only commercialized product, and absent the realization of sufficient revenues from product sales of Strimvelis or our current or future product candidates, if approved, we may never attain profitability in the future. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if, and as, we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Strimvelis in the European Union, and any product candidates for which we may submit for and obtain marketing approval anywhere in the world;
- continue our development of our product candidates, including continuing our ongoing advanced registrational trials and supporting studies of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and our ongoing clinical trials of OTL-102 for X-CGD and OTL-300 for transfusion-dependent beta-thalassemia, or TDBT, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- conduct investigational new drug application, or IND- or clinical trial application, or CTA-, CTA enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;

- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- develop, maintain, expand and protect our intellectual property portfolio; and
- transition our organization to being a public company.

Strimvelis is our only product that has been approved for sale and, to date, it has only been approved in the European Union for the treatment of ADA-SCID. Since receiving marketing authorization, only a limited number of patients have been treated with Strimvelis. We do not anticipate our revenue from sales of Strimvelis alone will be sufficient for us to become profitable. Under the terms of our asset purchase and license agreement with GSK, or the GSK Agreement, we are required to use our best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients, and at all times at the San Raffaele Hospital in Milan, Italy, provided that a minimum number of patients continue to be treated at this site. To become and remain profitable, we must develop and eventually commercialize product candidates with greater market potential. This will require us to be successful in a range of challenging activities, and our expenses will increase substantially as we seek to complete necessary preclinical studies and clinical trials of our product candidates, and manufacture, market and sell these or any future product candidates for which we may obtain marketing approval, if any, and satisfy any post-marketing requirements. We may never succeed in any or all of these activities and, even if we do, we may never generate revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our company also could cause you to lose all or part of your investment.

We have only generated revenue from sales of Strimvelis, and we may never be profitable.

Our ability to generate revenue from product sales and achieve profitability depends on our ability, alone or with collaborative partners, to successfully develop and commercialize products. Although we have begun generating revenue from the sale of Strimvelis, we do not expect to achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. For example, in connection with our transaction with GSK in April 2018, we expect to record a liability for Strimvelis representing the fair value of the future expected costs to maintain the marketing authorization in excess of expected future sales. Our ability to generate future revenues from product sales depends heavily on our and or our collaborators' success in:

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;

- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and compliance systems;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

We anticipate incurring significant costs associated with commercializing any products for which we obtain marketing approval. Our expenses could increase beyond expectations if we are required by the United States Food and Drug Administration, or the FDA, the European Medicines Agency, or the EMA, or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we continue to generate revenue from sales of Strimvelis and are able to generate revenues from the sale of any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

Even if this offering is successful, we will need additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

We expect our expenses to increase in connection with our ongoing activities, particularly as we continue the expansion of our commercial infrastructure in support of Strimvelis and our anticipated commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD, and OTL-103 for WAS, continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and continue to enhance and optimize our vector technology and manufacturing processes, including building our in-house drug product and vector manufacturing capabilities. In addition, we expect to incur significant expenses related to product sales, medical affairs, marketing, manufacturing, distribution and quality systems to support Strimvelis and any other products for which we obtain marketing approval. Furthermore,

upon the closing of this offering, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on reasonable terms, we would be forced to delay, reduce or eliminate certain of our research and development programs and/or commercialization efforts.

Our future capital requirements will depend on many factors, including:

- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution, to support Strimvelis in the European Union and any other products for which we obtain marketing approval;
- qualifying for, and maintaining adequate coverage and reimbursement by, government and payors on a timely basis for Strimvelis and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Strimvelis and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete. We may never generate the necessary data or results required to obtain marketing approval and achieve product sales for any products other than Strimvelis. In addition, Strimvelis or any other products for which we obtain marketing approval may not achieve commercial success. Any product revenues from our product candidates, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Raising additional capital may cause dilution to our existing shareholders, restrict our operations or cause us to relinquish valuable rights.

We may seek additional capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity, convertible debt securities or other equity-based derivative securities, your ownership interest will be diluted and the terms may include liquidation or other preferences that adversely affect your rights as a shareholder. Any indebtedness we incur would result in increased fixed payment obligations and could involve restrictive covenants, such as limitations on our ability to incur additional debt, limitations on our ability to acquire or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business. Furthermore, the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our ADSs to decline and existing shareholders may not agree with our financing plans or the terms of such financings. If we raise additional funds through strategic partnerships and alliances and licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, or our product candidates, or grant licenses on terms unfavorable to us. Adequate additional financing may not be available to us on acceptable terms, or at all.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We were incorporated in August 2018 to become a holding company for Orchard Therapeutics Limited, which was founded in 2015. Our operations, to date, have been limited to corporate organization, recruiting key personnel, business planning, raising capital, acquiring certain of our product candidate portfolios and rights to our technology, identifying potential product candidates, undertaking preclinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union and building a global commercial infrastructure to support anticipated commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved. We acquired Strimvelis in April 2018 and expect to submit a biologics license application, or BLA, for OTL-101 for ADA-SCID with the FDA in 2020, followed by a marketing authorization application, or MAA, submission with the EMA. We have not yet demonstrated the ability to complete clinical trials of our product candidates, obtain marketing approvals, manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make about our future success or viability may not be as accurate as they could be if we had a longer operating history. In addition, as a new business, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and setbacks.

Risks related to the discovery, development and regulatory approval of our product candidates

Our gene therapy product candidates are based on a novel technology, which makes it difficult to predict the time and cost of product candidate development and of subsequently obtaining regulatory approval.

We have concentrated our research and development efforts on our autologous *ex vivo* gene therapy approach, and our future success depends on our successful development of commercially viable gene therapy products. There can be no assurance that we will not experience problems or delays in developing new products and that such problems or delays will not cause unanticipated costs, or that any such development problems can be solved. Although we have established a commercial infrastructure for the production of Strimvelis in the European Union and we are building a global commercial infrastructure to support commercialization of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if such product candidates are approved, we may experience delays in developing a sustainable, reproducible and scalable manufacturing process or implementing that process in-house and at commercial partners, which may prevent us from commercializing our product candidates for which we obtain marketing approval on a timely or profitable basis, if at all.

In addition, the clinical trial requirements of the FDA, EMA and other foreign regulatory authorities and the criteria these regulators use to determine the safety and efficacy of a product candidate can vary substantially, for example, based upon the type, complexity, novelty and intended use and market of such product candidates. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or more extensively studied product candidates. To date, only a limited number of gene therapies have received marketing authorization from the FDA or EMA. We have limited experience in preparing, submitting and maintaining regulatory submissions, and have not previously submitted a BLA or MAA for any product candidate. It is difficult to determine how long it will take or how much it will cost to obtain regulatory approvals for our product candidates in the United States or the European Union or other jurisdictions or how long it will take to commercialize any other product candidates for which we obtain marketing approval. Approvals by the EMA may not be indicative of what the FDA may require for approval, and vice versa.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. Such requirements may lengthen the regulatory review process, require us to perform additional studies, and increase our development costs or may force us to delay, limit, or terminate certain of our programs.

Regulatory requirements governing gene and cell therapy products have evolved and may continue to change in the future. The FDA has established the Office of Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review when called upon. Gene therapy clinical trials conducted at institutions that receive funding for recombinant DNA research from the United States National Institutes of Health, or NIH, also are potentially subject to review by the NIH Office of Science Policy's Recombinant DNA Advisory Committee, or the RAC, in limited circumstances. Although the FDA decides whether individual gene therapy protocols may proceed, the RAC public review process, if undertaken, can delay the initiation of a clinical trial, even if the FDA has reviewed the trial design and details and authorized its initiation. Conversely,

the FDA can put an IND on clinical hold even if the RAC has provided a favorable review or an exemption from in-depth, public review. If we were to engage an NIH-funded institution, such as our partnership with The University of California Los Angeles, or UCLA, to conduct a clinical trial, that institution's institutional biosafety committee, or IBC, in addition to its institutional review board, or IRB, would need to review the proposed clinical trial protocol, patient informed consent, as well as other documentation of the safety profile of the drug candidate, to date, to assess the safety of the trial and may determine that RAC review is needed. In addition, adverse events in clinical trials of gene therapy products conducted by others may cause the FDA or other oversight bodies to change the requirements for approval of any of our product candidates, which could require additional preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapies and require that we comply with these new guidelines, which could require additional preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval.

The FDA, NIH and EMA have each expressed interest in further regulating biotechnology, including gene therapy and genetic testing. For example, the EMA advocates a risk-based approach to the development of a gene therapy product. Agencies at both the federal and state level in the United States, as well as the U.S. congressional committees and other governments or governing agencies, have also expressed interest in further regulating the biotechnology industry. Such action may delay or prevent commercialization of some or all of our product candidates.

These regulatory review committees and advisory groups and any new guidelines they promulgate may lengthen the regulatory review process, require us to perform additional studies, increase our development costs, lead to changes in regulatory positions and interpretations, delay or prevent approval and commercialization of these product candidates or lead to significant post-approval limitations or restrictions. As we advance our product candidates, we are required to consult with these regulatory and advisory groups, and comply with applicable guidelines. If we fail to do so, we may be required to delay or discontinue development of certain of our product candidates. These additional processes may result in a review and approval process that is longer than we otherwise would have expected. Delay or failure to obtain, or unexpected costs in obtaining, the regulatory approval necessary to bring a potential product to market could decrease our ability to generate sufficient product revenue, and our business, financial condition, results of operations and prospects would be materially and adversely affected.

The FDA recently released a series of draft guidances, which amongst other topics, included various aspects of gene therapy product development, review, and approval, including aspects relating to clinical and manufacturing issues related to gene therapy products. We cannot be certain whether future guidance will be issued and be relevant to, or have an impact on, our gene therapy programs or the duration or expense of any applicable regulatory development and review processes.

Our commercial product and product candidates and the process for administering our commercial product and product candidates may cause serious or undesirable side effects or adverse events or have other properties that could delay or prevent regulatory approval, limit commercial potential or result in significant negative consequences for our company.

Following treatment with our gene therapies, patients may experience changes in their health, including illnesses, injuries, discomforts or a fatal outcome. It is possible that as we test our product candidates in larger, longer and more extensive clinical programs, or as use of our product candidates becomes more widespread if they receive regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in previous clinical trials, as well as conditions that did not occur or went undetected in previous clinical trials, will be reported by patients. Gene therapies are also subject to the potential risk that occurrence of adverse events will be delayed following administration of the gene therapy due to persistent biological activity of the genetic material or other components of the vectors used to carry the genetic material. Many times, additional safety risks, contraindications, drug interactions, adverse events and side effects are only detectable after investigational products are tested in larger scale, registrational trials or, in some cases, after they are made available to patients on a commercial scale after approval. The FDA generally requires long-term follow-up of study subjects. Although the risk profile of a gene therapy candidate is a factor in determining the adequacy of such long-term follow-up, the FDA currently recommends that sponsors observe study subjects for potential gene therapy-related adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects. If additional experience indicates that any of our product candidates or similar products developed by other companies has side effects or causes serious or life-threatening side effects, the development of such product candidate may fail or be delayed, or, if the product has received regulatory approval, such approval may be revoked or limited.

There have been several adverse events and serious adverse events, or SAEs, attributed to gene therapy treatments in the past, including reported cases of leukemia with the use of gammaretrovirus vector and death seen in other clinical trials. Gene therapy is still a relatively new approach to disease treatment and additional adverse side effects could develop. Possible adverse side effects and adverse events that may occur with treatment with gene therapy products include an immunologic reaction early after administration that could substantially limit the effectiveness of the treatment or represent safety risks for patients. Another traditional safety concern for gene therapies using viral vectors has been the possibility of insertional mutagenesis by the vectors, leading to malignant transformation of transduced cells. While our gene therapy approach is designed to avoid immunogenicity after administration, there can be no assurance that patients would not develop antibodies that may impair treatment. Our approach involves the use of integrating vectors which have the potential for genomic disruption and therefore could interfere with other genes with adverse clinical effects. If any of our gene therapy product candidates demonstrates adverse side effects or adverse events at unacceptable rates or degrees of severity, we may decide or be required to halt or delay clinical development of such product candidates.

In addition to side effects and adverse events caused by our product candidates, the conditioning, administration process or related procedures also can cause adverse side effects and adverse events. A gene therapy patient is generally administered cytotoxic drugs to remove stem cells from the bone marrow to create sufficient space in the bone marrow for the modified stem

cells to engraft and produce new cells. This procedure compromises the patient's immune system. While certain of our product candidates are designed to utilize milder conditioning regimens that are intended to require only limited removal of a patient's bone marrow cells, the conditioning regimens may not be successful or may nevertheless result in adverse side effects and adverse events. If in the future we are unable to demonstrate that such adverse events were caused by the conditioning regimens used, or administration process or related procedure, the FDA, the European Commission, EMA or other regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all target indications. Even if we are able to demonstrate that adverse events are not related to the drug product or the administration of such drug product, such occurrences could affect patient recruitment, the ability of enrolled patients to complete the clinical trial, or the commercial viability of any product candidates that obtain regulatory approval.

Additionally, the FDA could require us to adopt a Risk Evaluation and Mitigation Strategy, or REMS, and other non-U.S. regulatory authorities could impose other specific obligations as a condition of approval to ensure that the benefits of our product candidates outweigh their risks, which may include, among other things, a medication guide outlining the risks of the product for distribution to patients, a communication plan to health care practitioners, and restrictions on how or where the product can be distributed, dispensed or used. Furthermore, if we or others later identify undesirable side effects caused by our commercial product or product candidates, several potentially significant negative consequences could result, including:

- regulatory authorities may suspend or withdraw approvals of such product or product candidate;
- regulatory authorities may require additional warnings or limitations of use in product labeling;
- we may be required to change the way a product candidate is distributed, dispensed, or administered or conduct additional clinical trials;
- we could be sued and held liable for harm caused to patients; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of Strimvelis and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

To date, most of the clinical trials for our product candidates were conducted as investigator-sponsored clinical trials using drug product manufactured at the academic sites. Regulatory authorities may closely scrutinize the data collected from these trials, and may require that we conduct additional clinical trials prior to any marketing approval.

We have limited experience conducting company-sponsored clinical trials and to date most of our product candidates have been evaluated under investigator-sponsored clinical trials using drug product manufactured at the applicable or relevant academic site. We did not control the design or administration of these investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these clinical trials. Investigator-sponsored clinical trials are often conducted under less rigorous clinical and manufacturing standards than those used in company-sponsored clinical trials. For example, the drug product used in our company-

sponsored clinical trials is manufactured by third party CMOs using current good manufacturing practices, or CGMP, standards. Accordingly, regulatory authorities may closely scrutinize the data collected from these investigator-sponsored clinical trials, and may require us to obtain and submit additional clinical data prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates. We will be required to demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CGMP-compliant CMOs. We may also be required to demonstrate improved quality and drug product manufacturing state of control in accordance with cGMP standards. For example, in the compassionate use program conducted by GOSH, one patient experienced an SAE, staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. A similar SAE, also staphylococcal infection, was observed in the clinical trial conducted at UCLA for OTL-101 with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. We believe that our commercial manufacturing processes for OTL-101 and our other product candidates, together with cryopreserved formulation, which allows for safety/microbiological testing to be completed prior to drug infusion to the patient, could mitigate the risk of such infections, but there can be no assurance that this will be the case. To the extent that the results of our current company-sponsored trials are inconsistent with, or different from, the results of any investigator-sponsored trials or raise concerns regarding our product candidates, the regulatory authorities may question the results from some or all of these trials, and may require us to obtain and submit additional clinical data from drug product manufactured by CGMP-compliant CMOs prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates.

The interim data and ad hoc analyses summarized in this prospectus are current as of the dates specified and are preliminary in nature. Our company-sponsored clinical trials of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and the investigator-sponsored clinical trials for OTL-102 for X-CGD and OTL-300 for TDBT are ongoing and not complete. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

From time to time, we may publish interim data and/or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as more patient data become available. In general, we seek to conduct interim analyses at times we pre-specify with the applicable regulators prior to commencement of the trial, at which time we lock and reconcile the database. We may from time to time elect not to conduct subsequent interim analyses so as not to compromise the statistical analysis plan for the trial. Accordingly, our interim analyses do not include data subsequent to the cut-off date and may not be available until the next planned interim analysis. From time to time, preliminary data and ad hoc analyses might be presented, typically by academic investigators at scientific conferences or in scientific publications.

With respect to clinical trials conducted by our academic or other collaborators, such as UCL, UCLA and GSK, we may not have access to the most recent clinical data or the clinical data available to us may otherwise be limited or incomplete. Interim data or ad hoc analyses from these clinical trials are not necessarily predictive of final results. Interim data or ad hoc analyses are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and/or more patient data become available to us. Interim, topline and preliminary data and ad hoc analyses also remain subject to audit and verification procedures

that may result in the final data being materially different from the preliminary data available to us or that we previously published. As a result, preliminary and interim data and ad hoc analyses should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the preliminary or interim data or ad hoc analyses could significantly harm our business prospects.

Similarly, the results of preclinical studies and previous clinical trials should not be relied upon as evidence that our ongoing or future clinical trials will succeed. Trial designs and results from preclinical studies or previous clinical trials are not necessarily predictive of future clinical trial results or the ability to obtain marketing approval for our product candidates. Our product candidates may fail to show the desired safety and efficacy in clinical development despite demonstrating positive results in preclinical studies or having successfully advanced through initial clinical trials or preliminary stages of registrational clinical trials.

For example, although sustained clinical activity has been observed in clinical trials to date for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS. Follow-up in each of these clinical trials is ongoing and there can be no assurance that the results, in each case as of the applicable primary endpoint measurement date, seen in clinical trials of any of our product candidates ultimately will result in success in clinical trials or marketing approvals. These data, or other positive data, may not continue or occur for these patients or for any future patients in our ongoing or future clinical trials, and may not be repeated or observed in ongoing or future trials involving our product candidates. There is limited data concerning long-term safety and efficacy following treatment with our product candidates. OTL-201 for mucopolysaccharidosis type III A, or MPS-IIIA, and OTL-202 for mucopolysaccharidosis type III B, or MPS-IIIB, have not yet been tested in humans. These and any of our other product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in preclinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

Favorable results from compassionate use programs may not establish proof of concept, and the FDA or other regulatory authorities may not accept compassionate use data as sufficient clinical validation in support of our regulatory approval efforts.

A number of patients have been administered our autologous *ex vivo* gene therapies through compassionate use programs. Compassionate use is a term that is used to refer to the use of an investigational drug outside of a clinical trial to treat a patient with a serious or immediately life-threatening disease or condition who has no comparable or satisfactory alternative treatment options. Regulators often allow compassionate use on a case-by-case basis for an individual patient or for defined groups of patients with similar treatment needs. Caution should be given when reviewing and interpreting compassionate use data. While results from treating patients through compassionate use have in certain cases been encouraging, we cannot be assured that the results observed in these cases will be observed in our ongoing or future clinical trials or that our ongoing and future clinical trials will ultimately be successful.

We plan to submit any data available to us from compassionate use cases as part of any regulatory submission for the applicable product candidate. However, because these patients

were not treated as part of a clinical trial in accordance with the procedures set forth under the applicable clinical trial protocol, regulatory authorities may not accept compassionate use data as sufficient clinical validation in support of our regulatory approval efforts, or they may find that the data submitted from our clinical trials are insufficient to support approval. Such decisions could materially and adversely affect our business, financial condition, results of operations and prospects.

We may find it difficult to enroll patients in our clinical trials, which could delay or prevent us from proceeding with clinical trials of our product candidates.

Identifying and qualifying patients to participate in clinical trials of our product candidates is critical to our success. The timing of our clinical trials depends on our ability to recruit patients to participate as well as the completion of required follow-up periods. Patients may be unwilling to participate in our gene therapy clinical trials because of negative publicity from adverse events related to the biotechnology or gene therapy fields, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. In addition, the indications that we are currently targeting and may in the future target are rare diseases, which may limit the pool of patients that may be enrolled in our ongoing or planned clinical trials. The timeline for recruiting patients, conducting trials and obtaining regulatory approval of our product candidates may be delayed, which could result in increased costs, delays in advancing our product candidates, delays in testing the effectiveness of our product candidates or termination of the clinical trials altogether.

We may not be able to identify, recruit and enroll a sufficient number of patients, or those with the required or desired characteristics, to complete our clinical trials in a timely manner. For example, due to the nature of the indications that we are initially targeting, patients with advanced disease progression may not be suitable candidates for treatment with our product candidates and may be ineligible for enrollment in our clinical trials. Therefore, early diagnosis in patients with our target diseases is critical to our success. Patient enrollment and trial completion is affected by factors including the:

- size of the patient population and process for identifying subjects;
- design of the trial protocol;
- eligibility and exclusion criteria;
- safety profile, to date, of the product candidate under study;
- perceived risks and benefits of the product candidate under study;
- perceived risks and benefits of gene therapy-based approaches to treatment of diseases, including any required pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject’s disease at the time of enrollment;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- ability to obtain and maintain subject consent;
- risk that enrolled subjects will drop out before completion of the trial;

- patient referral practices of physicians; and
- ability to monitor subjects adequately during and after treatment.

Our current product candidates are being developed to treat rare conditions. We plan to seek initial marketing approvals in the United States and the European Union. We may not be able to initiate or continue clinical trials if we cannot enroll a sufficient number of eligible patients to participate in the clinical trials required by the FDA or the EMA. Our ability to successfully initiate, enroll and complete a clinical trial in any foreign country is subject to numerous risks unique to conducting business in foreign countries, including:

- difficulty in establishing or managing relationships with academic partners or contract research organizations, or CROs, and physicians;
- different standards for the conduct of clinical trials;
- the absence in some countries of established groups with sufficient regulatory expertise for review of gene therapy protocols;
- our inability to locate qualified local consultants, physicians and partners; and
- the potential burden of complying with a variety of foreign laws, medical standards and regulatory requirements, including the regulation of pharmaceutical and biotechnology products and treatment.

If we have difficulty enrolling a sufficient number of patients to conduct our clinical trials as planned, we may need to delay, limit or terminate ongoing or planned clinical trials, any of which would have an adverse effect on our business, financial condition, results of operations and prospects.

We may encounter substantial delays in our clinical trials or we may fail to demonstrate safety and efficacy to the satisfaction of applicable regulatory authorities.

Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, time-consuming and uncertain as to outcome. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. A failure of one or more clinical trials can occur at any stage of testing. Events that may prevent successful or timely completion of clinical development include:

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required IRB approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our clinical trials;
- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and recordkeeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;

- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

If the results of our clinical trials are inconclusive or if there are safety concerns or adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with, or later become subject to, labeling or a REMS that includes significant use or distribution restrictions or safety warnings, precautions, contraindications, drug interactions, or adverse events;
- be subject to changes with the way the product is administered;
- be required to perform additional clinical trials to support comparability or approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product or impose restrictions on its distribution in the form of a REMS;
- be sued by competitors, patent holders, patients, or third-parties; or
- experience damage to our reputation.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

We may elect to initiate a rolling BLA for our product candidates, in which case the FDA will not complete, and may delay initiating, its review of the BLA until we submit all of the required information.

A rolling BLA is an application process that allows us to submit the information required by the BLA in sections. The FDA will not complete, and may delay initiating, its review of our BLA until

we submit all of the required information for a full BLA. If we are delayed or unable to provide this required information it could delay or prevent our ability to obtain regulatory approvals, as a result of which our business, prospects, financial condition and results of operations may suffer.

The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates. Before we submit our product candidates for marketing approval, the FDA and/or the EMA may require us to conduct additional clinical trials, or evaluate patients for an additional follow-up period.

The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS may not be sufficiently robust to support the submission of marketing approval for our product candidates. The FDA normally requires two registrational trials to approve a drug or biologic product, and thus the FDA may require that we conduct additional clinical trials of our product candidates prior to a BLA submission. The FDA typically does not consider a single clinical trial to be adequate to serve as a registrational trial unless it is, among other things, well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome, and a confirmatory study would be practically or ethically impossible. Additionally, while the FDA recognizes the potential for natural history models to augment the need for placebo arms in trials for drugs that target very rare disease, where trial recruitment can be especially challenging, the FDA has found the use of natural history data as a historical comparator to be unsuitable for adequate and well-controlled trials in many circumstances. The FDA generally finds trials using historical controls to be credible only when the observed effect is large in comparison to variability in disease course.

Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study is not practicable for ethical and other reasons. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data, to provide clinically meaningful results. Additionally, even though OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS have achieved the primary endpoints in their respective ongoing clinical trials, neither the FDA nor EMA have approved the primary endpoints and data in these trials and, therefore, it is still possible that the FDA or EMA may require us to conduct a second registrational trial, possibly involving a larger sample size or a different clinical trial design, particularly if the FDA or EMA does not find the results from these trials to be sufficiently persuasive to support a BLA or MAA submission, as applicable. The FDA or EMA may also require that we conduct a longer follow-up period of patients treated with our product candidates prior to accepting our BLA or MAA submission, as applicable.

In addition, data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. We also may experience regulatory delays or rejections as a result of many factors, including SAEs involving our product candidates, changes in regulatory policy or changes in requirements during the period of our product candidate development. Any such delays could materially and adversely affect our business, financial condition, results of operations and prospects.

We expect that the FDA and EMA will assess the totality of the safety and efficacy data from our product candidates in reviewing any future BLA or MAA submissions. Based on this assessment, the FDA or EMA may require that we conduct additional preclinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications.

It is possible that the FDA or the EMA may not consider the results of our clinical trials to be sufficient for approval of our product candidates. If the FDA or the EMA requires additional trials, we would incur increased costs and delays in the marketing approval process, which may require us to expend more resources than we have available. In addition, it is possible that the FDA and the EMA may have divergent opinions on the elements necessary for a successful BLA and MAA, respectively, which may cause us to alter our development, regulatory and/or commercialization strategies.

Most of the clinical trials for our product candidates conducted to date were conducted at sites outside the United States, and the FDA may not accept data from trials conducted in such locations.

To date, most of the clinical trials conducted on our product candidates were conducted outside the United States. For example, we do not yet have an IND open in the United States for OTL-200 for MLD, OTL-103 for WAS or OTL-300 for TDBT. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, it would likely result in the need for additional trials, which would be costly and time-consuming and would delay or permanently halt our development of the applicable product candidates.

In addition, in order to commence a clinical trial in the United States, we are required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar CTA we submit in other countries, will be accepted. We may also be required to conduct additional preclinical testing prior to submitting an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a BLA submission and approval of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product and/or demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CMOs. Failure to demonstrate such comparability could adversely affect our ability to secure regulatory approval for our product candidates, or could adversely affect the commercial viability of our product candidates if approved for use using only HSCs derived using bone marrow and/or fresh drug product.

To date, most of the patients who have been treated in clinical trials involving our product candidates received fresh drug product manufactured using HSCs derived from the patient's bone marrow at academic centers. We are currently evaluating our product candidates and plan to seek marketing approval using drug product that is manufactured at CMOs using HSCs derived from either the patient's bone marrow or mobilized peripheral blood and using a procedure by which the gene-modified HSCs are cryopreserved in order to maintain the cellular material in suitable condition until it is thawed prior to being infused into the patient.

In those cases where clinical trials were conducted using vector and/or drug product manufactured at academic research centers, we will need to demonstrate comparability between vector and drug product manufactured by our CMOs with vector and/or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another and in some cases we may elect to initially seek approval of our product candidate using one cellular source only, and subsequently seek approval for the use of the other cellular source. For example, in the case of OTL-101, pending the outcome of ongoing regulatory discussions, we may initially seek approval of OTL-101 using patient bone marrow and subsequently seek approval for the use of mobilized peripheral blood. We plan to submit analytical comparability analyses as part of our future regulatory submissions, and in some cases we are conducting clinical trials in order to generate clinical data to support these analytical comparability analyses. We cannot assure you that the FDA, EMA or other regulatory authority will not require us to conduct additional analytical comparability analyses, preclinical studies and/or clinical trials before approving our product candidates using these production methods and processes. Moreover, we cannot assure you that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval or our product candidates using these production methods and processes. For example, both the FDA and the EMA has advised us that it will require clinical data using drug product that has been cryopreserved as part of our planned BLA and MAA submissions for OTL-103 for WAS. In addition, we are conducting a clinical trial at UCLA using a cryopreserved formulation of OTL-101 (with bone marrow as the cellular source). In this trial, one of the 10 patients treated with this formulation failed to engraft, although we do not believe engraftment failure was due to use of a cryopreserved formulation.

If the FDA, EMA or other regulatory authority does not accept our comparability data, our regulatory approval for such product candidate, if any, will be limited or delayed. For example, if one or more of these regulatory authorities does not accept that our cryopreservation process produces a product candidate that is comparable to our fresh drug product, our regulatory approval, if any, would be limited to our fresh product candidate until we are able to provide the

regulator with satisfactory comparability data, which may include data from additional clinical trials. Similarly, if one or more of these regulatory authorities does not accept that our drug product manufactured with HSCs derived from the patient's mobilized peripheral blood is comparable to drug product manufactured with HSCs derived from the patient's bone marrow, our regulatory approval, if any, would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulator with satisfactory comparability data, which may include data from additional clinical trials. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

Even if we complete the necessary preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate and the approval may be for a more narrow indication than we seek.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved the product candidate. Even if our product candidates demonstrate safety and efficacy in clinical trials, the regulatory agencies may not complete their review processes in a timely manner, or we may not be able to obtain regulatory approval. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

In addition, regulatory agencies may not approve the labeling claims that are necessary or desirable for the successful commercialization of our product candidates. For example, regulatory agencies may approve a product candidate for fewer or more limited indications than requested or may grant approval subject to the performance of post-marketing studies. Regulators may approve a product candidate for a smaller patient population (such as pre-symptomatic MLD patients as opposed to symptomatic patients), drug formulation (such as drug product using HSCs derived from bone marrow as opposed to mobilized peripheral blood or vice versa) or manufacturing processes (such as fresh drug product as opposed to cryopreserved), than we are seeking. If we are unable to obtain necessary regulatory approvals, or more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

Even if we complete the necessary preclinical studies and clinical trials, the marketing approval process is expensive, time-consuming and uncertain and may prevent us from obtaining approvals for the commercialization of some or all of our product candidates. If we or any future collaborators are not able to obtain, or if there are delays in obtaining, required regulatory approvals, we or they will not be able to commercialize our product candidates, and our ability to generate revenue will be materially impaired.

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing such

product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process.

Securing marketing approval requires the submission of extensive preclinical and clinical data and supporting information to the various regulatory authorities for each therapeutic indication to establish the product candidate's safety and efficacy. Securing regulatory approval also requires the submission of extensive information about the product manufacturing process and controls up to and including inspection of manufacturing facilities by, the relevant regulatory authority. Our product candidates may not be effective, may be only moderately effective or may prove to have undesirable or unintended side effects, toxicities or other characteristics that may preclude our obtaining marketing approval or prevent or limit commercial use.

The process of obtaining marketing approvals, both in the United States and abroad, is expensive (the submission fee in the United States is more than $2.0 million and may be higher in the future), may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type, complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a drug candidate. Any marketing approval of our product candidates that we, or any future collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

Accordingly, if we or any future collaborators experience delays in obtaining approval or if we or they fail to obtain approval of our product candidates, the commercial prospects for our product candidates may be harmed and our ability to generate revenues will be materially impaired.

While we intend to seek designations for our product candidates with the FDA and comparable other regulatory authorities that are intended to confer benefits such as a faster development process or an accelerated regulatory pathway, there can be no assurance that we will successfully obtain such designations. In addition, even if one or more of our product candidates are granted such designations, we may not be able to realize the intended benefits of such designations.

The FDA and comparable other regulatory authorities offer certain designations for product candidates that are designed to encourage the research and development of product candidates that are intended to address conditions with significant unmet medical need. These designations may confer benefits such as additional interaction with regulatory authorities, a potentially accelerated regulatory pathway and priority review. OTL-101 for ADA-SCID has received a Breakthrough Therapy Designation from the FDA, but there can be no assurance that we will successfully obtain such designation for any of our other product candidates. In addition, while such designations could expedite the development or approval process, they generally do not change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

For example, we may seek a Breakthrough Therapy Designation for some of our other product candidates. A breakthrough therapy is defined as a therapy that is intended, alone or in combination with one or more other therapies, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the therapy may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For therapies that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Therapies designated as breakthrough therapies by the FDA are also eligible for accelerated approval. Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a Breakthrough Therapy Designation for a product candidate may not result in a faster development process, review or approval compared to therapies considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that such product candidates no longer meet the conditions for qualification.

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a “rare pediatric disease” as a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be received from sales in the U.S. of such drug. Under the FDA’s Rare Pediatric Disease Priority Review Voucher, or PRV, program, upon the approval of a BLA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a Rare Pediatric Disease PRV that can be used to obtain priority review for a subsequent new drug application or BLA. The PRV may be sold or transferred an unlimited number of times. Congress has extended the PRV program until September 30, 2020, with potential for PRVs to be granted until 2022. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

In addition, we may seek Fast Track Designation for some of our product candidates. If a therapy is intended for the treatment of a serious or life-threatening condition and the therapy demonstrates the potential to address unmet medical needs for this condition, the therapy sponsor may apply for Fast Track Designation. The FDA has broad discretion whether or not to grant this designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track Designation does not provide assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

In addition, we may seek a regenerative medicine advanced therapy, or RMAT, designation for some of our product candidates. An RMAT is defined as cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. Gene therapies, including genetically modified cells that lead to a durable modification of cells or tissues may meet the definition of a regenerative medicine therapy. The RMAT program is intended to facilitate efficient development and expedite review of RMATs, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and for which preliminary clinical evidence indicates that the drug has the potential to address unmet medical needs for such disease or condition. A BLA for an RMAT may be eligible for priority review or accelerated approval. An RMAT may be eligible for priority review if it treats a serious condition, and, if approved would provide a significant improvement in the safety or effectiveness of the treatment of the condition. An RMAT may be eligible for accelerated approval through (1) surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit or (2) reliance upon data obtained from a meaningful number of sites. Benefits of such designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence, clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. RMAT designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for designation as a RMAT, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of RMAT designation for a product candidate may not result in a faster development process, review or approval compared to drugs considered for approval under conventional FDA procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as for RMAT designation, the FDA may later decide that the biological products no longer meet the conditions for qualification.

We may seek priority review designation for one or more of our product candidates, but we might not receive such designation, and even if we do, such designation may not lead to a faster regulatory review or approval process.

If the FDA determines that a product candidate offers a treatment for a serious condition and, if approved, the product would provide a significant improvement in safety or effectiveness, the FDA may designate the product candidate for priority review. A priority review designation means that the goal for the FDA to review an application is six months, rather than the standard review period of ten months. We may request priority review for our product candidates. The FDA has broad discretion with respect to whether or not to grant priority review status to a product candidate, so even if we believe a particular product candidate is eligible for such designation or status, in particular if such product candidate has received a Breakthrough Therapy designation or RMAT designation, the FDA may decide not to grant it. Moreover, a priority review designation does not result in expedited development and does not necessarily result in expedited regulatory review or approval process or necessarily confer any advantage with respect to approval compared to conventional FDA procedures. Receiving priority review from the FDA does not guarantee approval within the six-month review cycle or at all.

Under the terms of the GSK Agreement, we are required to use commercially reasonable efforts to obtain a PRV from the FDA for each of OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT

and to transfer the first such PRV to GSK. GSK also has an option to acquire at a defined price any PRV granted to us thereafter for OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT. In the event that GSK does not exercise this option with respect to any PRV, we may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK.

We have sought and received orphan drug designation for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-102 for X-CGD and OTL-300 for TDBT from the EMA, but we may be unable to obtain orphan drug designation for our other product candidates and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union, EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the European Union. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the European Union would be sufficient to justify the necessary investment in developing the drug or biologic product.

We have sought and received orphan drug designation for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-102 for X-CGD and OTL-300 for TDBT from the EMA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our product candidates such designation. Additionally, the designation of any of our product candidates as an orphan product does not mean that any regulatory agency will accelerate regulatory review of, or ultimately approve, that product candidate, nor does it limit the ability of any regulatory agency to grant orphan drug designation to product candidates of other companies that treat the same indications as our product candidates prior to our product candidates receiving exclusive marketing approval.

Generally, if a product candidate with an orphan drug designation receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA or EMA from approving another marketing application for a product that constitutes the same drug treating the same indication for that marketing exclusivity period, except in limited circumstances. If another sponsor receives such approval before we do (regardless of our orphan drug designation), we will be precluded from receiving marketing approval for our product for the applicable exclusivity period. The applicable period is seven years in the United States and 10 years in the European Union. The exclusivity period in the European Union can be reduced to six years if a product no longer meets the criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency

determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the European Union, marketing authorization may be granted to a similar medicinal product for the same orphan indication if:

- the second applicant can establish in its application that its medicinal product, although similar to the orphan medicinal product already authorized, is safer, more effective or otherwise clinically superior;
- the holder of the marketing authorization for the original orphan medicinal product consents to a second orphan medicinal product application; or
- the holder of the marketing authorization for the original orphan medicinal product cannot supply sufficient quantities of orphan medicinal product.

Even if we obtain and maintain approval for our product candidates in one jurisdiction, we may never obtain approval for our product candidates in other jurisdictions, which would limit our market opportunities and adversely affect our business.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by the EMA or other regulatory authorities in other countries or jurisdictions, and approval by the EMA or another regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our product candidates outside of the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable regulatory authorities of foreign countries also must approve the manufacturing and marketing of the product candidates in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for any of our product candidates may be withdrawn. If we fail to comply with the regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects will be harmed.

Additionally, on June 23, 2016, the electorate in the United Kingdom voted in favor of leaving the European Union, commonly referred to as Brexit. On March 29, 2017, the country formally notified the European Union of its intention to withdraw pursuant to Article 50 of the Lisbon Treaty. Since a significant proportion of the regulatory framework in the United Kingdom is derived from European Union directives and regulations, the referendum could materially impact the regulatory regime with respect to the approval of our product candidates in the United Kingdom or the European Union. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the United Kingdom and/or the European Union and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom and/or European Union for our product candidates, which could significantly and materially harm our business.

We may seek a conditional marketing authorization in Europe for some or all of our current product candidates, but we may not be able to obtain or maintain such designation.

As part of its marketing authorization process, the EMA may grant marketing authorizations for certain categories of medicinal products on the basis of less complete data than is normally required, when doing so may meet unmet medical needs of patients and serve the interest of public health. In such cases, it is possible for the Committee for Medicinal Products for Human Use, or CHMP, to recommend the granting of a marketing authorization, subject to certain specific obligations to be reviewed annually, which is referred to as a conditional marketing authorization. This may apply to medicinal products for human use that fall under the jurisdiction of the EMA, including those that aim at the treatment, the prevention, or the medical diagnosis of seriously debilitating or life-threatening diseases and those designated as orphan medicinal products.

A conditional marketing authorization may be granted when the CHMP finds that, although comprehensive clinical data referring to the safety and efficacy of the medicinal product have not been supplied, all the following requirements are met:

- the risk-benefit balance of the medicinal product is positive;
- it is likely that the applicant will be in a position to provide the comprehensive clinical data;
- unmet medical needs will be fulfilled; and
- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data is still required.

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing

trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

Granting a conditional marketing authorization allows medicines to reach patients with unmet medical needs earlier than might otherwise be the case and will ensure that additional data on a product is generated, submitted, assessed and acted upon. Although we may seek a conditional marketing authorization for one or more of our product candidates by the EMA, the CHMP may ultimately not agree that the requirements for such conditional marketing authorization have been satisfied and hence delay the commercialization of our product candidates.

Even if we obtain regulatory approval for a product candidate, our products will remain subject to regulatory oversight.

Strimvelis and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates also may be subject to a REMS, limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the quality, safety and efficacy of the product. For example, in the United States, the holder of an approved BLA is obligated to monitor and report adverse events and any failure of a product to meet the specifications in the BLA. FDA guidance advises that patients treated with some types of gene therapy undergo follow-up observations for potential adverse events for as long as 15 years. The holder of an approved BLA also must submit new or supplemental applications and obtain FDA approval for certain changes to the approved product, product labeling or manufacturing process. Advertising and promotional materials must comply with FDA rules and are subject to FDA review, in addition to other potentially applicable federal and state laws.

In the European Union, the advertising and promotion of our products are subject to European Union laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual European Union Member States may apply to the advertising and promotion of medicinal products. These laws require that promotional materials and advertising for medicinal products are consistent with the product's Summary of Product Characteristics, or SmPC, as approved by the competent authorities. The SmPC is the document that provides information to physicians concerning the safe and effective use of the medicinal product. It forms an intrinsic and integral part of the marketing authorization granted for the medicinal product. Promotion of a medicinal product that does not comply with the SmPC is considered to constitute off-label promotion. The off-label promotion of medicinal products is prohibited in the European Union. The applicable laws at European Union level and in the individual European Union Member States also prohibit the direct-to-consumer advertising of prescription-only medicinal products. Violations of the rules governing the promotion of medicinal products in the European Union could be penalized by administrative measures, fines and imprisonment. These laws may further limit or restrict the advertising and promotion of our products to the general public and may also impose limitations on our promotional activities with health care professionals.

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance CGMP requirements and adherence to commitments made in the BLA or foreign

marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of any of our product candidates, a regulatory authority may:

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and adversely affect our business, financial condition, results of operations and prospects.

In addition, the FDA's policies, and those of the EMA and other regulatory authorities, may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would materially and adversely affect our business, financial condition, results of operations and prospects.

Both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual European Union Member States both before and after grant of the manufacturing and marketing authorizations. This includes control of compliance with CGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third-party manufacturers would be required to ensure that all of our processes, quality systems, methods, and equipment are compliant with CGMP. Failure by us or by any of our third-party partners, including suppliers, manufacturers, and distributors to comply with

European Union laws and the related national laws of individual European Union Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, European Union legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that EMA and the competent authorities of the European Union Member States have the authority to require companies to conduct additional post-approval clinical efficacy and safety studies. The legislation also governs the obligations of marketing authorization holders with respect to additional monitoring, adverse event management and reporting. Under the pharmacovigilance legislation and its related regulations and guidelines, we may be required to conduct a burdensome collection of data regarding the risks and benefits of marketed products and may be required to engage in ongoing assessments of those risks and benefits, including the possible requirement to conduct additional clinical trials, which may be time-consuming and expensive and could impact our profitability. Non-compliance with such obligations can lead to the variation, suspension or withdrawal of marketing authorization or imposition of financial penalties or other enforcement measures.

We face significant competition in our industry and there can be no assurance that our product candidates, if approved, will achieve acceptance in the market over existing established therapies. In addition, our competitors may develop therapies that are more advanced or effective than ours, which may adversely affect our ability to successfully market or commercialize any of our product candidates.

We operate in a highly competitive segment of the biopharmaceutical market. We face competition from many different sources, including larger pharmaceutical, specialty pharmaceutical and biotechnology companies, as well as from academic institutions, government agencies and private and public research institutions. Our product candidates, if successfully developed and approved, will compete with established therapies, some of which are being marketed by large and international companies. In addition, we expect to compete with new treatments that are under development or may be advanced into the clinic by our competitors. There are a variety of product candidates, including gene therapies, in development for the indications that we are targeting.

We rely primarily on know-how and trade secret protection for aspects of our proprietary technologies, our commercial product Strimvelis and our product candidates. We do not have any issued patents covering our commercial product Strimvelis or our product candidates, and only one patent family with patent applications pending in the United States and Europe with patent claims directed to our OTL-101 product candidate and its use in the treatment of ADA-SCID. This means that barriers to entry that typically apply in the case of pharmaceutical and biopharmaceutical companies with issued patents covering aspects of their proprietary technologies, products and product candidates, such as composition of matter claims, will generally not apply to our commercial product or our product candidates, and this may expose us to intense competition from other biopharmaceutical companies, particularly those companies that possess greater financial

resources and more mature product candidate development, manufacturing, marketing and distribution resources than we do. Although our product candidates, if approved, may be eligible for marketing and/or data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial product or one or more of our product candidates, the result of which could have a material adverse effect on our business.

For example, bluebird bio is developing Lentiglobin, a lentiviral-based autologous *ex vivo* gene therapy for TDBT. In October 2018, bluebird bio announced that the EMA had accepted its MAA for Lentiglobin for the treatment of adolescents and adults with TDBT and a non-ß0/ß0 genotype. bluebird bio has publicly announced its intention to file a BLA in the United States for Lentiglobin in the future. This product candidate has been granted orphan drug status by both the FDA and EMA for the treatment of beta-thalassemia, Fast Track Designation by the FDA for the treatment of beta-thalassemia major, Breakthrough Therapy Designation by the FDA for the treatment of transfusion-dependent patients with beta-thalassemia major and Priority Medicines (PRIME) scheme by the EMA for the treatment of TDBT. If bluebird bio's product candidate receives marketing approval in the European Union or the United States, these designations may delay or prevent our ability to commercialize OTL-300 for TDBT for the applicable periods.

Other pharmaceutical and biotechnology companies that we expect to compete with include:

- **ADA-SCID:** Adagen, marketed by Leadiant Biosciences, is the only approved enzyme replacement therapy, or ERT, for ADA-SCID. We are aware that Leadiant Biosciences has filed a supplement BLA for elapegademase, a pegylated recombinant version of Adagen, for the treatment of ADA-SCID.
- **MLD:** We are aware that the Institut National de la Santé Et de la Recherche Médicale and Bicêtre hospital in Paris are investigating intracerebral gene therapy for MLD using an adeno-associated viral, or AAV-, 10 vector in a clinical trial. We are also aware that Shire is investigating ERT for MLD with a biweekly intrathecal infusion. We are also aware that Shenzhen University is evaluating a lentiviral *ex vivo* gene therapy for MLD.
- **WAS:** We are aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with autologous *ex vivo* lentiviral gene therapy.
- **X-CGD:** We are aware that Généthon is sponsoring a clinical trial with autologous *ex vivo* lentiviral gene therapy in France, to which we have certain rights.
- **TDBT:** In addition to bluebird bio, we are aware that Memorial Sloane Kettering Cancer Center has been conducting a clinical trial utilizing a lentiviral vector. In addition, we are aware that Sangamo is investigating zinc finger nuclease-mediated gene-correction techniques in TDBT. Several other groups are developing gene editing approaches for beta-thalassemia, including CRISPR Therapeutics, EDITAS and Intellia Therapeutics. CRISPR Therapeutics' CTA for its gene editing approach for beta-thalassemia was approved in 2018. Several other approaches are under investigation to improve treatment outcomes in beta-thalassemia.

In addition, many universities and private and public research institutes are active in our target disease areas.

Many of our competitors have significantly greater financial, product candidate development, manufacturing and marketing resources than we do. Large pharmaceutical and biotechnology companies have extensive experience in clinical testing and obtaining regulatory approval for their products, and mergers and acquisitions within these industries may result in even more resources being concentrated among a smaller number of larger competitors. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our business would be materially and adversely affected if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, have broader market acceptance, are more convenient or are less expensive than any product candidate that we may develop.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances.

Our focus on developing our current product candidates may not yield any commercially viable products, and our failure to successfully identify and develop additional product candidates could impair our ability to grow.

As part of our growth strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates for ADA-SCID, MLD, WAS, X-CGD and TDBT. We may spend several years completing our development of any particular current or future product candidates, and failure can occur at any stage. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential than OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS or our other product candidates. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

Because our internal research capabilities are limited, we may be dependent upon biotechnology companies, academic scientists and other researchers to sell or license product candidates, approved products or the underlying technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising product candidates and products.

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as ERT. We have not yet succeeded and may never succeed in demonstrating efficacy and safety of our product candidates or any future product candidates in clinical trials or in obtaining marketing approval thereafter. For example, although we acquired Strimvelis, we have not yet obtained regulatory approval to sell any of our other product candidates based on our therapeutic approaches. Accordingly, our focus on treating rare diseases may not result in the discovery and development of commercially viable products.

If we are unsuccessful in our development efforts, we may not be able to advance the development of our product candidates, commercialize products other than Strimvelis, raise capital, expand our business or continue our operations.

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial product or our product candidates or otherwise harm our business.

Biological products are inherently difficult to manufacture, and gene therapy products are complex biological products, the development and manufacture of which necessitates substantial expertise and capital investment. Strimvelis and our product candidates are individually manufactured for each patient using complex processes in specialized facilities. Our production process requires a variety of raw materials, some of which are highly specialized, including the viral vector that encodes for the functional copy of the missing or faulty gene to treat a specific disease. Some of these raw materials have limited and, in some cases, sole suppliers. Even though we plan to have back-up supplies of raw materials whenever possible, we cannot be certain such supplies will be sufficient if our primary sources are unavailable. A shortage of a critical raw material or a technical issue during manufacturing may lead to delays in clinical development or commercialization of our product candidates. Additionally, production difficulties caused by unforeseen events may delay the availability of one or more of the necessary raw materials or delay the manufacture of our product candidates for use in clinical trials or for commercial supply.

We have contracted with third party CMOs for the manufacture of our viral vectors and drug product. We expect these CMOs will be capable of providing sufficient quantities of our viral vectors and gene therapy products to meet the anticipated scales for our clinical trials and current and initial commercial demands, if approved. However, to meet our projected needs for further commercial manufacturing and clinical trials of new product candidates, third parties with whom we currently work might need to increase their scale and frequency of production or we will need to secure alternate suppliers or have in-house capabilities. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements, although we cannot be certain that identifying and establishing relationships with such sources, if necessary, would not result in significant delay or material additional costs.

We have limited experience manufacturing our product candidates. We may be unable to produce clinical or commercial viral vectors or Strimvelis or our product candidates or meet demand to support a clinical trial or a commercial launch for our product candidates. Any such failure could delay or prevent the development of our product candidates and would have a negative impact on our business, financial condition and results of operations.

Additionally, the manufacturers of pharmaceutical products must comply with strictly enforced CGMP requirements, state and federal regulations, as well as foreign requirements when applicable. Any failure of us or our CMOs to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical trials. If we or our manufacturers were to fail to comply with the FDA, EMA, or other regulatory authority, it could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of raw materials, product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. Our potential future dependence upon others for the manufacture of our gene therapies may also adversely affect our future profit margins and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis.

Delays in obtaining regulatory approval of our or our CMOs' manufacturing process and facility or disruptions in our manufacturing process may delay or disrupt our commercialization efforts. Until recently, no CGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product.

Before we can begin to commercially manufacture our viral vector or product candidates in our own facility, or the facility of a CMO, we must obtain regulatory approval from the FDA for our manufacturing processes and for the facility in which manufacturing is performed. A manufacturing authorization must also be obtained from the appropriate European Union regulatory authorities. Until recently, no CGMP gene therapy manufacturing facility in the United States had received approval from the FDA for the manufacture of an approved gene therapy product and, therefore, the timeframe required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our or our CMOs manufacturing facility by the FDA and other relevant regulatory authorities before any of our gene therapy product candidates can obtain marketing approval. In order to obtain approval, we will need to ensure that all of our processes, quality systems, methods, equipment policies and procedures are compliant with CGMP, and perform extensive audits of vendors, contract laboratories, CMOs and suppliers. If any of our vendors, contract laboratories, CMOs or suppliers is found to be out of compliance with CGMP, we may experience delays or disruptions in manufacturing while we work with these third parties to remedy the violation or while we work to identify suitable replacement vendors. The CGMP requirements govern quality control of the manufacturing process and documentation policies and procedures. In complying with CGMP, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. If we fail to comply with these requirements, we would be subject to possible regulatory action and may not be permitted to sell any products that we may develop.

Failure to comply with ongoing regulatory requirements could cause us to suspend production or put in place costly or time-consuming remedial measures.

The regulatory authorities may, at any time following approval of a product for sale, audit the manufacturing facilities for such product. If any such inspection or audit identifies a failure to comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the

temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon our CMOs or us could harm our business, financial condition, results of operations and prospects.

If our CMOs or we fail to comply with applicable CGMP regulations, FDA and foreign regulatory authorities can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product candidate or suspension or revocation of a pre-existing approval. Such an occurrence may cause our business, financial condition, results of operations and prospects to be harmed.

Additionally, if supply from any CMO or us is delayed or interrupted, there could be a significant disruption in the clinical or commercial supply of our product candidates. We have agreements in place with our CMOs pursuant to which we are collaborating on CGMP manufacturing processes and analytical methods for the manufacture and release of our viral vectors and drug product. Therefore, if we are unable to enter into an agreement with our CMOs to manufacture clinical or commercial material for our product programs, or if our agreement with our CMOs were terminated, we would have to find suitable alternative manufacturers. This could delay our or our collaborators' ability to conduct clinical trials or commercialize our current and future product candidates. The regulatory authorities also may require additional clinical trials and other nonclinical and or analytical evaluations if a new manufacturer is relied upon for clinical or commercial production. Switching manufacturers may involve substantial costs, require significant comparability studies and could result in a delay in our desired clinical and commercial timelines.

We are planning to establish our own manufacturing facility and infrastructure in addition to or in lieu of relying on CMOs for the manufacture of our viral vectors and product candidates, which will be costly, time-consuming, and which may not be successful.

We have entered into a letter of intent to lease a 152,995 square foot facility located in Fremont, California to renovate as an alternative or in addition to our reliance on CMOs, for the manufacture of our viral vectors and product candidates. If the lease is executed, we plan to renovate and customize the facility for the manufacture of lentiviral vectors and product candidates. We expect that development of our own manufacturing facility will provide us with enhanced control of material supply for both clinical trials and commercialization, enable the more rapid implementation of process changes, and allow for better long-term margins. However, we have no experience as a company in developing a manufacturing facility and may never be successful in developing our own manufacturing facility or capability. Furthermore, we will need to hire additional personnel to manage our operations and facilities and develop the necessary infrastructure to continue the development, and eventual commercialization, if approved, of our product candidates. We, as a company, have no experience in setting up, building or eventually managing a manufacturing facility. If we failed to select the correct location, or if we fail to complete the planned lease, or fail to complete the planned renovation and customization in an efficient manner, or fail to recruit the required personnel and generally manage our growth effectively, the development and production of our viral vectors and product candidates could be curtailed or delayed. We may establish multiple manufacturing facilities as we expand our commercial footprint to multiple geographies, which may lead to regulatory delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

In addition, the FDA, the EMA and other foreign regulatory authorities may require us to submit samples of any lot of any approved product together with the protocols showing the results of applicable tests at any time. Under some circumstances, the FDA, the EMA or other foreign regulatory authorities may require that we not distribute a product lot until the relevant agency authorizes its release. Slight deviations in the manufacturing process, including those affecting quality attributes and stability, may result in unacceptable changes in a viral vector or a gene therapy product that could result in lot failures or product recalls. Lot failures or product recalls could cause us to delay product launches or clinical trials, which could be costly to us and otherwise harm our business, financial condition, results of operations and prospects. Problems in our manufacturing processes could restrict our ability to meet market demand for our products.

We also may encounter problems hiring and retaining the experienced technical, quality control, quality assurance and manufacturing personnel needed to operate our manufacturing processes and facilities, which could result in delays in production or difficulties in maintaining compliance with applicable regulatory requirements.

Any problems in our manufacturing process or facilities could make us a less attractive collaborator for potential partners, including larger pharmaceutical companies and academic research institutions, which could limit our access to additional attractive development programs.

We do not have experience as a company managing a manufacturing facility and complex supply chain.

Operating our own manufacturing facility will require significant resources, and we do not have experience as a company in managing a manufacturing facility and complex supply chain. In part because of this lack of experience, we cannot be certain that our manufacturing plans will be completed on time, if at all, or if manufacturing of product candidates from our own manufacturing facility for our planned clinical trials will begin or be completed on time, if at all. In part because of our inexperience, we may have unacceptable or inconsistent product quality success rates and yields, and we may be unable to maintain adequate quality control, quality assurance, manufacturing, technical or other qualified personnel. In addition, if we switch from our current CMOs to our own manufacturing facility for one or more of our product candidates in the future, we may need to conduct additional preclinical, analytical or clinical trials to bridge our modified product candidates to earlier versions. Failure to successfully obtain and operate our planned manufacturing facility could adversely affect the commercial viability of our product candidates.

Patients' cellular source material must be transported from the clinical collection site to the manufacturing facility and the cryopreserved drug product must be returned to the clinical site for administration into the patient using controlled temperature shipping containers.

Once collected from the patient, the cellular source material must be transported to the manufacturing facility using a shipping container that maintains the material at a cool temperature and be delivered typically within three days of collection. While we intend to use reputable couriers and agents for the transport of such materials, if the shipping container is opened or damaged such that the cool temperature is not maintained, the cellular source material may be adversely impacted and it may not be feasible to manufacture a drug product for the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, other events or held up at a customs point, the cellular source material may not be delivered within a time window that will allow for its use for the successful manufacture of a drug product.

Similarly, the patient's autologous drug product must be returned to the clinical site for administration into the patient using a specialized shipping container that maintains the material at a very low temperature for a period of typically up to ten days. While we intend to use reputable couriers and agents for the transport of our drug products, if the shipping container is opened or damaged such that the very low temperature is not maintained, the drug product may be adversely impacted and it may not be feasible to administer it to the patient or, if administered, it could cause harm to the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, held up at a customs point or other events, and is not delivered to the clinical site within the time period that the very low temperature is maintained, the drug product may be adversely affected and be unable to be administered or, if administered, could cause harm to the patient.

Any of the above events, should they happen, could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Our gene therapies are for autologous use only. Therefore, if a drug product is administered to the wrong patient, the patient could suffer harm.

Our gene therapies are autologous, so they must be administered back only to the patient from which the cellular source material was collected. While we implement specific identifiers, lot numbers and labels with cross checks for our products and operations from collection of cellular source material, through manufacture of drug product, transport of product to the clinical site up to thawing and administration of the product, it is possible that a product may be administered into the wrong patient. If an autologous gene therapies were to be administered into the wrong patient, the patient could suffer harm, including experiencing a severe adverse immune reaction and this event, should it happen, could adversely affect our business, financial condition, results of operations and prospects.

Any microbial contamination in the manufacturing process for our viral vectors or drug product, shortages of raw materials or failure of any of our key suppliers to deliver necessary components could result in delays in our clinical development or marketing schedules.

Given the nature of biologics manufacturing, there is a risk of microbial contamination. Any microbial contamination could adversely affect our ability to produce, release or administer our gene therapies on schedule and could, therefore, harm our results of operations and cause reputational damage. Additionally, although our gene therapies are tested for microbial contamination prior to release, if a contaminated product was administered to a patient, it could result in harm to the patient.

Some of the raw materials required in our manufacturing processes are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our vectors or drug product could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

Interruptions in the supply of viral vectors and/or drug products or inventory loss may harm our operating results and financial condition.

Our viral vectors and drug products are manufactured using technically complex processes in specialized facilities, sometimes using specialized equipment with highly specific raw materials

and other production constraints. The complexity of these processes, as well as strict government standards for the manufacture and storage of our gene therapies, subjects us to manufacturing risks. While viral vectors and drug product released for use in clinical trials or for commercialization undergo sample testing, some defects may only be identified following their release. In addition, process deviations or unanticipated effects of approved process changes may result in viral vector and/or drug product not complying with stability requirements or specifications. Our viral vectors and drug product must be stored and transported at temperatures within a certain range. If these environmental conditions deviate, our viral vectors and drug products' remaining shelf-lives could be impaired or their efficacy and safety could be negatively impacted, making them no longer suitable for use. For example, patients' cellular material must be received by the manufacturing facility typically within three days after collection, and our gene therapy must be received by the clinical site typically within ten days after shipping from the manufacturing facility. The occurrence, or suspected occurrence, of manufacturing and distribution difficulties can lead to lost inventories and, in some cases, product recalls, with consequential reputational damage and the risk of product liability. The investigation and remediation of any identified problems can cause production delays, substantial expense, lost sales and delays of new product launches. Any interruption in the supply of finished products or the loss thereof could hinder our ability to timely distribute our products and satisfy customer demand. Any unforeseen failure in the storage of the viral vectors or drug products or loss in supply could delay our clinical trials and result in a loss of our market share for our commercial product or our product candidates, if approved, and negatively affect our business, financial condition, results of operations and prospects.

Our cryopreserved product candidates require specific storage, handling and administration at the clinical sites.

Our cryopreserved product candidates must be stored at very low temperatures in specialized freezers or specialized shipping containers until immediately prior to use. For administration, the cryopreserved drug product container must be carefully removed from storage, and rapidly thawed using a thawing device or water bath in an area proximal to the patient's bedside and administered into the patient. The handling, thawing and administration of the cryopreserved gene therapy product must be performed according to specific instructions, typically using specific disposables and in some steps within specific time periods. Failure to correctly handle the product, follow the instructions for thawing and administration and or failure to administer the product within the specified period post-thaw could negatively impact the efficacy and or safety of the product.

Risks related to our reliance on third parties

We have in the past, and in the future may, enter into collaborations with third parties to develop or commercialize product candidates. If these collaborations are not successful, our business could be adversely affected.

We have entered into licensing and collaboration agreements with third parties, including the GSK Agreement, pursuant to which GSK transferred to us Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT. In addition GSK novated to us their R&D and collaboration and license agreement, or the R&D Agreement, with Telethon-OSR, which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Italy for MPS-I, CGD and globoid cell leukodystrophy, or GLD. These agreements impose, and we expect

that future license agreements will impose, various due diligence, milestone payment, royalty, insurance and other obligations on us. The termination of these agreements could result in our loss of rights to practice the intellectual property licensed to us under these agreements, and could compromise our development and commercialization efforts for our current or any future product candidates. See the section of this prospectus titled “Business—license agreements” for a more detailed description of our current license agreements.

We may also enter into additional collaborations in the future. We have limited control over the amount and timing of resources that our current and future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our and our collaborators’ abilities to successfully perform the functions assigned to each of us in these arrangements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

We may potentially enter into additional collaborations with third parties in the future. Any future collaborations we enter into in the future may pose several risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- we may not achieve any milestones, or receive any milestone payments, under our collaborations, including milestones and/or payments that we expect to achieve or receive;
- the clinical trials conducted as part of these collaborations may not be successful;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborators’ strategic focus or available funding or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for clinical trials, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- we may not have access to, or may be restricted from disclosing, certain information regarding product candidates being developed or commercialized under a collaboration and, consequently, may have limited ability to inform our shareholders about the status of such product candidates;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- product candidates developed in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or products, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of any such product candidate;
- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development of any product candidates, may cause delays or termination of the research, development or commercialization of such product candidates, may lead to additional responsibilities for us with respect to such product candidates or may result in litigation or arbitration, any of which would be time-consuming and expensive;
- collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;
- disputes may arise with respect to the ownership of intellectual property developed pursuant to our collaborations;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

If our collaborations do not result in the successful development and commercialization of products, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this prospectus apply to the activities of our collaborators.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. These relationships, or those like them, may require us to incur non-recurring and other charges, increase our near- and long-term expenditures, issue securities that dilute our existing shareholders or disrupt our management and business. In addition, we could face significant competition in seeking appropriate collaborators and the negotiation process is time-consuming and complex. Our ability to reach a definitive collaboration agreement will depend, among other things, upon our assessment of the collaborator’s resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator’s evaluation of several factors. If we license rights to product candidates, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate them with our existing operations and company culture.

We utilize, and expect to continue to utilize, third parties to conduct some or all aspects of our vector production and product manufacturing for the foreseeable future, and these third parties may not perform satisfactorily.

Until such time as we establish our manufacturing facility that has been properly commissioned to comply with CGMP requirements, we will not be able to independently manufacture material for our planned clinical programs or our commercial supply, Strimvelis or any other product for which we obtain marketing approval. We currently rely on our CMOs and in some cases academic partners for the production of our viral vectors and product candidates for our ongoing registrational and clinical trials and preclinical studies. For future clinical trials and for products for which we obtain marketing approval, we intend to utilize materials manufactured by CGMP-compliant CMOs. If our academic partners or these CMOs do not successfully carry out their contractual duties, meet expected deadlines or manufacture our viral vector and product candidates in accordance with regulatory requirements or if there are disagreements between us and our academic partners or these CMOs, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or preclinical data. In such instances, we may need to enter into an appropriate replacement third-party relationship, which may not be readily available or available on acceptable terms, which would cause additional delay or increased expense prior to the approval of our product candidates and would thereby have a negative impact on our business, financial condition, results of operations and prospects.

We have partnered with commercial CGMP-compliant CMOs, and intend to utilize viral vectors and gene therapy products manufactured by such CMOs for our future clinical trials and products for which we obtain marketing approval. In some cases, we may need to perform clinical or analytical or other animal or cell-based testing to demonstrate that materials produced by these CMOs, or any other third-party manufacturer that we engage, is comparable to the material produced by our academic partners and utilized in our registrational and clinical trials of our product candidates. There is no assurance that these CMOs, or any other future third-party manufacturer that we engage, will be successful in producing any or all of our viral vector or product candidates, that any such product will, if required, pass the required comparability testing, or that any materials produced by these CMOs or any other third-party manufacturer that we engage will have the same effect in patients that we have observed to date with respect to materials produced by our academic partners. We believe that our manufacturing network will have sufficient capacity to meet demand for our clinical and existing and expected initial commercial needs, but there is a risk that if supplies are interrupted or result in poor yield or quality, it would materially harm our business. Additionally, if the gene therapy industry were to grow, we may encounter increasing competition for the raw materials and consumables necessary for the production of our product candidates. Furthermore, demand for CMO CGMP manufacturing capabilities may grow at a faster rate than existing manufacturing capacity, which could disrupt our ability to find and retain third-party manufacturers capable of producing sufficient quantities of our viral vectors or product candidates for future clinical trials or to meet expected initial commercial demand.

Under certain circumstances, our current CMOs are entitled to terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our development activities. Our reliance on our CMOs for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations.

In addition to our current CMOs, we may rely on additional third parties to manufacture ingredients of our viral vectors and or drug product in the future and to perform quality testing, and reliance on these third parties entails risks to which we would not be subject if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize any of our product candidates. Some of these events could be the basis for FDA, EMA or other regulatory authority action, including injunction, recall, seizure or total or partial suspension of product manufacture.

We rely on third parties, including independent clinical investigators and CROs, to conduct and sponsor some of the clinical trials of our product candidates. Any failure by a third party to meet its obligations with respect to the clinical development of our product candidates may delay or impair our ability to obtain regulatory approval for our product candidates.

We have relied upon and plan to continue to rely upon third parties, including independent clinical investigators and third-party CROs, to conduct our preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing preclinical and clinical programs. For example, OTL-300 for TDBT is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy, and OTL-102 for X-CGD is currently being investigated in ongoing academic-sponsored clinical trials at Boston Children's Hospital, the NIH and UCLA in the United States, and GOSH in Europe. Additionally, our registrational trial of OTL-101 for ADA-SCID was sponsored by UCLA. While we will have agreements governing the activities of our academic partners and CROs, we will control only certain aspects of their activities and have limited influence over their actual performance.

Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, or EEA, and comparable foreign regulatory authorities for all of our products in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, principal investigators and trial sites. If we fail to exercise adequate oversight over any of our academic partners or CROs or if we or any of our academic partners or CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements, or for any other reasons, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before

approving our marketing applications. We cannot assure you that upon a regulatory inspection of us, our academic partners or our CROs or other third parties performing services in connection with our clinical trials, such regulatory authority will determine that any of our clinical trials complies with GCP regulations. In addition, our clinical trials must be conducted with product produced under applicable CGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase, and our ability to generate revenues could be delayed.

We do not control the design or conduct of the academic-sponsored trials, and it is possible that the FDA or EMA will not view these academic-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. Such arrangements provide us certain information rights with respect to the academic-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the academic-sponsored trials. However, we do not have control over the timing and reporting of the data from academic-sponsored trials, nor do we own the data from the academic-sponsored trials. If we are unable to confirm or replicate the results from the academic-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of OTL-300 for TDBT or OTL-102 for X-CGD. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the firsthand knowledge we might have gained had the academic-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected.

Additionally, the FDA or EMA may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these academic-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these academic-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional preclinical, manufacturing, or clinical data.

We and our contract manufacturers are subject to significant regulation with respect to manufacturing our viral vectors and drug products. The manufacturing facilities on which we rely may not continue to meet regulatory requirements and have limited capacity.

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and drug product. Each supplier may require licenses to manufacture such components if such processes are not owned by the supplier or in the public domain and we may be unable to transfer or sublicense the intellectual property rights we may have with respect to such activities.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CMOs for our viral vectors and drug product, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials, including in some cases critical raw materials used in the manufacture thereof, must be manufactured in accordance with CGMP. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our viral vectors or product candidates that may not be detectable in final product testing. We or our CMOs must supply all necessary documentation in support of a

BLA or MAA on a timely basis and must adhere to the FDA's and EMA's good laboratory practices, or GLP, GMP and other applicable regulations enforced, in the case of the FDA, through its facilities inspection program. Some of our CMOs have not produced a commercially-approved product and have never been inspected by the FDA or other regulatory body. Our facilities and quality systems and the facilities and quality systems of some or all of our CMOs must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our viral vector or drug product or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted. If these facilities do not pass a pre-approval plant inspection, FDA or other regulatory body approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, audit our manufacturing facilities or those of our CMOs. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our CMOs fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be materially harmed.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals of our product candidates or commercialization of our commercial product or product candidates, if approved, cause us to incur higher costs and prevent us from commercializing our products successfully. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our preclinical studies and clinical trials may be delayed.

We are dependent on a limited number of suppliers and, in some instances, a sole supplier, for some of our components and materials used in our product candidates.

We currently depend on a limited number of suppliers and, in some instances, a sole supplier, for some of the components and equipment necessary for the production of our viral vectors and drug product. We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a sole or a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components, and in some cases, no alternatives. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply

from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

If we are required to switch to a replacement supplier, the manufacture and delivery of our viral vectors and product candidates could be interrupted for an extended period, adversely affecting our business. Establishing additional or replacement suppliers may not be accomplished quickly. If we are able to find a replacement supplier, the replacement supplier would need to be qualified and may require additional regulatory authority approval, which could result in further delay. For example, the FDA or EMA could require additional supplemental data, manufacturing data and comparability data up to and including clinical trial data if we rely upon a new supplier. While we seek to maintain adequate inventory of the components and materials used in our product candidates, any interruption or delay in the supply of components or materials, or our inability to obtain components or materials from alternate sources at acceptable prices in a timely manner, could impair our ability to conduct our clinical trials and, if our product candidates are approved, to meet the demand of our customers and cause them to cancel orders.

In addition, as part of the FDA's approval of our product candidates, the FDA must review and approve the individual components of our production process, which includes raw materials, the manufacturing processes and facilities of our suppliers. Some of our current suppliers have not undergone this process nor have they had any components included in any product approved by the FDA.

Our reliance on these suppliers subjects us to a number of risks that could harm our reputation, business, and financial condition, including, among other things:

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;
- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

If any of these risks materialize, costs could significantly increase and our ability to conduct our clinical trials and, if our product candidates are approved, to meet demand for our products could be impacted.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to manufacture our vectors and our commercial product and product candidates, and because we collaborate with various organizations and academic institutions on the advancement of our gene therapy approach, we must, at times, share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our collaborators, advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, such as trade secrets.

Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our collaborators, advisors, employees and consultants to publish data potentially relating to our trade secrets. Our academic collaborators typically have rights to publish data, provided that we are notified in advance and may delay publication for a specified time in order to secure our intellectual property rights arising from the collaboration. In other cases, publication rights are controlled exclusively by us, although in some cases we may share these rights with other parties. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of these agreements, independent development or publication of information including our trade secrets in cases where we do not have proprietary or otherwise protected rights at the time of publication. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks related to commercialization of our product candidates

We currently have limited sales and marketing capabilities. If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates that may be approved, we may not be successful in commercializing our product candidates if and when approved, and we may be unable to generate any product revenue.

If our product candidates are approved for commercialization, we currently intend to seek to commercialize them in the United States and Europe directly with specialized teams, given the relative rarity of the indications we are targeting. We currently have a limited marketing and sales team for the marketing, sales and distribution of our commercial product and our product candidates, if approved. In order to commercialize Strimvelis and OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if approved, or any of our other product candidates that may be approved, we must build, on a territory-by-territory basis, marketing, sales, distribution,

managerial and other capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a commercial organization is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- the inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or persuade adequate numbers of physicians to prescribe any future product that we may develop;
- the lack of complementary treatments to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability to us from these revenue streams is likely to be lower than if we were to market and sell any product candidates that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties and any of them may fail to devote the necessary resources and attention to sell and market our product candidates effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates.

Our efforts to educate the medical community and payors on the benefits of our product candidates may require significant resources given the relative rarity of the indications we are targeting, and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our product candidates and the indications we are targeting. Even if our product candidates are approved, if we are unable to successfully market our products, we will not be able to generate significant revenues from such products, if approved.

If we are unable to expand our market development capabilities or enter into agreements with third parties to market and sell any of our product candidates for which we obtain marketing approval, we will be unable to generate any product revenue.

To successfully commercialize any products that may result from our development programs, we need to continue to expand our market development capabilities, either on our own or with others. The development of our own market development effort is, and will continue to be, expensive and time-consuming and could delay any product launch. Moreover, we cannot be

certain that we will be able to successfully develop this capability. We may enter into collaborations regarding any approved product candidates with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we will be unable to generate sufficient product revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded sales, distribution and marketing operations to recruit, hire, train and retain marketing and sales personnel. We also face competition in our search for third parties to assist us with the sales and marketing efforts of our product candidates, if approved. Without an internal team or the support of a third-party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

If the market opportunities for our product candidates are smaller than we believe they are, our product revenues may be adversely affected and our business may suffer.

We focus our research and product development on treatments for primary immune deficiencies, inherited metabolic and neurodegenerative genetic disorders and rare inherited blood disorders. Our understanding of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates may prove to be incorrect and new studies may reduce the estimated incidence or prevalence of these diseases. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, we may not address the entirety of the opportunity we are seeking. As a result, the number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our products or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects.

The commercial success of any current or future product candidate will depend upon the degree of market acceptance by physicians, patients, payors and others in the medical community.

Even if we obtain any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting gene therapy products in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors and others in the medical community. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

- the potential efficacy and potential advantages over alternative treatments;
- the frequency and severity of any side effects, including any limitations or warnings contained in a product’s approved labeling;
- the frequency and severity of any side effects resulting from the conditioning regimen or follow-up requirements for the administration of our product candidates;
- the relative convenience and ease of administration;

- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

Even if a product candidate displays a favorable efficacy and safety profile in preclinical studies and clinical trials, market acceptance of the product, if approved for commercial sale, will not be known until after it is launched. Our efforts to educate the medical community and payors on the benefits of our product candidates may require significant resources and may never be successful. Such efforts to educate the marketplace may require more resources than are required by the conventional technologies marketed by our competitors. If these products do not achieve an adequate level of acceptance, we may not generate significant product revenue and may not become profitable.

The insurance coverage and reimbursement status of newly-approved products is uncertain. Failure to obtain or maintain adequate coverage and reimbursement for any of our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve market approval. The availability and extent of reimbursement by governmental and private payors is essential for most patients to be able to afford expensive treatments, such as stem cell transplants. Sales of our product candidates will depend substantially, both domestically and abroad, on the extent to which the costs of our product candidates will be paid by health maintenance, managed care, pharmacy benefit and similar healthcare management organizations, or reimbursed by government health administration authorities, private health coverage insurers and other payors. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement. If reimbursement is not available, or is available only at limited levels, we may not be able to successfully commercialize our product candidates, if approved. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize a sufficient return on our investment.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the U.S. Department of Health and Human Services, as the CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare. Private payors tend to follow the CMS to a substantial degree. It is difficult to predict what the CMS will decide with respect to reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products.

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and

reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

Moreover, efforts by governmental and payors, in the United States and abroad, to cap or reduce healthcare costs may cause such organizations to limit both coverage and level of reimbursement for new products approved and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of any of our product candidates, due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the entry of new products.

Due to the novel nature of our technology and the potential for our product candidates to offer therapeutic benefit in a single administration, we face uncertainty related to pricing and reimbursement for these product candidates.

We are targeting rare diseases for which the patient populations are relatively small. In addition, treatment with any of our product candidates involves only a single administration. As a result, the pricing and reimbursement of our product candidates, if approved, must be adequate to support commercial infrastructure. It is possible that commercially available products may serve as a reference price that, for various reasons, may be lower than the price we need to obtain for our product candidates. If we are unable to obtain adequate levels of reimbursement, our ability to successfully market and sell our product candidates will be adversely affected. The manner and level at which reimbursement is provided for services related to our product candidates (e.g., for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates, if approved.

Healthcare legislative reform measures and constraints on national budget social security systems may have a material adverse effect on our business and results of operations.

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the

Patient Protection and Affordable Care Act or the PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars; addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjected manufacturers to new annual fees and taxes for certain branded prescription drugs; and provided incentives to programs that increase the federal government's comparative effectiveness research. Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 12, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, the CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces. Congress may consider other legislation to replace elements of the ACA.

The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device exercise tax on non-exempt medical devices. Further, the BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. Thus, the full impact of the ACA, any law replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain

in effect through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at broadening the availability of healthcare and containing or lowering the cost of healthcare. We cannot predict the initiatives that may be adopted in the future. The continuing efforts of the government, insurance companies, managed care organizations and other payors of healthcare services to contain or reduce costs of healthcare and/or impose price controls may adversely affect:

- the demand for our product candidates, if we obtain regulatory approval;
- our ability to set a price that we believe is fair for our products;
- our ability to generate revenue and achieve or maintain profitability;
- the level of taxes that we are required to pay; and
- the availability of capital.

Any denial in coverage or reduction in reimbursement from Medicare or other government programs may result in a similar denial or reduction in payments from private payors, which may adversely affect our future profitability.

Risks related to our business operations

Our future results will suffer if we do not effectively manage our expanded operations as a result of our recent acquisition of Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT.

We acquired worldwide rights to Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT in April 2018 pursuant to the GSK Agreement. The GSK Agreement significantly changed the composition of our operations, markets and product candidate mix. Our future success depends, in part, on our ability to address these changes, and, where necessary, to attract and retain new personnel that possess the requisite skills called for by these changes.

Our failure to adequately address the financial, operational or legal risks of our acquisition of Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT, or any future acquisitions, license arrangements, other strategic transactions could harm our business. Financial aspects of these transactions that could alter our financial position, reported operating results or ADS price include:

- use of cash resources;
- higher than anticipated acquisition costs and expenses;
- potentially dilutive issuances of equity securities;
- the incurrence of debt and contingent liabilities, impairment losses or restructuring charges;

- large write-offs and difficulties in assessing the relative percentages of in-process research and development expense that can be immediately written off as compared to the amount that must be amortized over the appropriate life of the asset; and
- amortization expenses related to other intangible assets.

Operational risks that could harm our existing operations or prevent realization of anticipated benefits from these transactions include:

- challenges associated with managing an increasingly diversified business;
- disruption of our ongoing business;
- difficulty and expense in assimilating the operations, products, technology, information systems or personnel of the acquired company;
- entry into a geographic or business market in which we have little or no prior experience;
- inability to maintain uniform standards, controls, procedures and policies;
- the assumption of known and unknown liabilities of the acquired business or asset, including intellectual property claims; and
- subsequent loss of key personnel.

Our future success depends, in part, upon our ability to manage our expansion opportunities. Integrating new operations into our existing business in an efficient and timely manner, successfully monitoring our operations, costs, regulatory compliance and customer relationships, and maintaining other necessary internal controls pose substantial challenges for us. As a result, we cannot assure you that our expansion or acquisition opportunities will be successful, or that we will realize our expected operating efficiencies, cost savings, revenue enhancements, synergies or other benefits.

Our gene therapy approach utilizes vectors derived from viruses, which may be perceived as unsafe or may result in unforeseen adverse events. Negative public opinion and increased regulatory scrutiny of gene therapy and genetic research may damage public perception of our product candidates or adversely affect our ability to conduct our business or obtain regulatory approvals for our product candidates.

Gene therapy remains a novel technology, with only a limited number of gene therapy products approved to date. Public perception may be influenced by claims that gene therapy is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. In particular, our success will depend upon physicians specializing in the treatment of those diseases that our product candidates target prescribing treatments that involve the use of our product candidates in lieu of, or in addition to, existing treatments they are already familiar with and for which greater clinical data may be available. More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products we may develop. For example, earlier gene therapy trials led to several well-publicized adverse events, including cases of leukemia and death seen in other trials using other vectors. Adverse events in our clinical trials, even if not ultimately attributable to our product candidates (such as the many adverse events that typically arise from the conditioning process), or adverse events in other lentiviral gene therapy trials, and the resulting publicity could result in increased

governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our potential product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates.

Increasing demand for compassionate use of our unapproved therapies could result in losses.

We are developing our autologous *ex vivo* gene therapies to address rare diseases for which there are currently limited or no available therapeutic options. Recent media attention to individual patients' expanded access requests has resulted in the introduction and/or passage of legislation at the local and national level referred to as "Right to Try" laws which are intended to help enable patients access to unapproved therapies. Such legislation includes the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, which was signed into law on May 30, 2018. New and emerging legislation regarding expanded access to unapproved drugs for life-threatening illnesses could negatively impact our business in the future.

A possible consequence of both activism and legislation in this area is the need for us to initiate an unanticipated expanded access program or to make our product candidates more widely available sooner than anticipated. We have limited resources and unanticipated trials or access programs could result in diversion of resources from our primary goals.

In addition, patients who receive access to unapproved drugs through compassionate use or expanded access programs have life-threatening illnesses and have exhausted all other available therapies. The risk for SAEs in this patient population is high which could have a negative impact on the safety profile of our product candidates, which could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

Our future success depends on our ability to retain key employees, consultants and advisors and to attract, retain and motivate qualified personnel.

We are highly dependent on principal members of our executive team and key employees, including our Chief Executive Officer and Chief Scientific Officer the loss of whose services may adversely impact the achievement of our objectives. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives. Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

If we are unable to manage expected growth in the scale and complexity of our operations, our performance may suffer.

If we are successful in executing our business strategy, we will need to expand our managerial, operational, financial and other systems and resources to manage our operations, continue our research and development activities and continue to build a commercial infrastructure to support commercialization of Strimvelis and any of our product candidates that are approved for sale. Future growth would impose significant added responsibilities on members of management. It is likely that our management, finance, development personnel, systems and facilities currently in place may not be adequate to support this future growth. Our need to effectively manage our operations, growth and product candidates requires that we continue to develop more robust business processes and improve our systems and procedures in each of these areas and to attract and retain sufficient numbers of talented employees. We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our research, development and growth goals.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA, EMA or of other foreign regulatory authorities, provide accurate information to the FDA, EMA and other foreign regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. We plan to adopt a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We are subject to the U.K. Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or the FCPA, and other anti-corruption laws, as well as export control laws, import and customs laws, trade and economic sanctions laws and other laws governing our operations.

Our operations are subject to anti-corruption laws, including the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing,

promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

We are also subject to other laws and regulations governing our international operations, including regulations administered by the governments of the United Kingdom and the United States, and authorities in the European Union, including applicable export control regulations, economic sanctions and embargoes on certain countries and persons, anti-money laundering laws, import and customs requirements and currency exchange regulations, collectively referred to as the Trade Control laws.

There is no assurance that we will be completely effective in ensuring our compliance with all applicable anti-corruption laws, including the Bribery Act, the FCPA or other legal requirements, including Trade Control laws. If we are not in compliance with the Bribery Act, the FCPA and other anti-corruption laws or Trade Control laws, we may be subject to criminal and civil penalties, disgorgement and other sanctions and remedial measures, and legal expenses, which could have an adverse impact on our business, financial condition, results of operations and liquidity. Likewise, any investigation of any potential violations of the Bribery Act, the FCPA, other anti-corruption laws or Trade Control laws by United Kingdom, United States or other authorities could also have an adverse impact on our reputation, our business, results of operations and financial condition.

We may be subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws health information privacy and security laws, and other health care laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

If we obtain FDA approval for any of our product candidates and begin commercializing those products in the United States, our operations will be directly, or indirectly through our prescribers, customers and purchasers, subject to various federal and state fraud and abuse laws and regulations, including, without limitation, the federal Health Care Program Anti-Kickback Statute, the federal civil and criminal False Claims Act and Physician Payments Sunshine Act and regulations. These laws will impact, among other things, our proposed sales, marketing and educational programs. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct our business. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, the purchase, lease, order, arrangement, or recommendation of any good, facility, item or service for which payment may be made, in whole or in part,

under a federal healthcare program, such as the Medicare and Medicaid programs. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties;

- the federal civil and criminal false claims laws and civil monetary penalty laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information;
- The U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;
- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payer. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, any of which could adversely affect our ability to operate our business and our financial results.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of Strimvelis or our product candidates harms patients, or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of Strimvelis or any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. There is a risk that our product candidates may induce adverse events. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- the impairment of our business reputation;
- the withdrawal of clinical trial participants;
- costs due to related litigation;
- the distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We believe our product liability insurance coverage is sufficient in light of our current commercial and clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage each time we commercialize an additional product; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claim or series of claims brought against us could cause our ADS price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with the diseases targeted by certain of our product candidates are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life- threatening health risks. During the course of treatment, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our products, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our products, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our sales efforts, delay our regulatory approval process in other countries, or impact and limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties. Furthermore, environmental laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

As a company based outside of the United States, our business is subject to economic, political, regulatory and other risks associated with international operations.

As a company based in the United Kingdom, our business is subject to risks associated with conducting business outside of the United States. Many of our suppliers and clinical trial relationships are located outside the United States. Accordingly, our future results could be harmed by a variety of factors, including:

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;

- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the eligible members of the U.K. electorate for the United Kingdom to withdraw from the European Union;
- trade protection measures, import or export licensing requirements or other restrictive actions by governments;
- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business, which could reduce the price of our ADSs.

In June 2016, a majority of the eligible members of the electorate in the United Kingdom voted to withdraw from the European Union in a national referendum, commonly referred to as Brexit. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to Article 50 of the EU Treaty, unless the European Council, in agreement with the United Kingdom, unanimously decides to extend this period. On March 29, 2017, the U.K. Prime Minister formally delivered the notice of withdrawal. It appears likely that this withdrawal will involve a process of lengthy negotiations between the United Kingdom and EU Member States to determine the future terms of the United Kingdom's relationship with the European Union.

These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global

financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the EEA overall could be diminished or eliminated.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of Brexit, the United Kingdom could lose the benefits of global trade agreements negotiated by the European Union on behalf of its members, which may result in increased trade barriers that could make our doing business in Europe more difficult. In addition, currency exchange rates in the pound sterling and the euro with respect to each other and the U.S. dollar have already been adversely affected by Brexit. Furthermore, at present, there are no indications of the effect Brexit will have on the pathway to obtaining marketing approval for any of our product candidates in the United Kingdom, or what, if any, role the EMA may have in the approval process.

We or the third parties upon whom we depend may be adversely affected by earthquakes or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Earthquakes or other natural disasters could severely disrupt our operations, and have a material adverse effect on our business, results of operations, financial condition and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure, such as the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place currently are limited and are unlikely to prove adequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business, financial condition, results of operations and prospects.

Exchange rate fluctuations may materially affect our results of operations and financial condition.

Owing to the international scope of our operations, fluctuations in exchange rates, particularly between the pound sterling and the U.S. dollar, may adversely affect us. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and

other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. dollar, but also the euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our product development programs.

Despite our security measures, our internal computer systems and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. If any cyberattack or data breach were to occur in the future and cause interruptions in our or our collaborators', contractors' or consultants' operations, it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Risks related to our intellectual property

We may become subject to claims that we are infringing certain third party patents, for example, patents relating to lentiviral vectors, or other third party intellectual property rights, any of which may prevent or delay our development and commercialization efforts and have a material adverse effect on our business.

Our commercial success depends in part on avoiding infringing, misappropriating and otherwise violating the patents and other intellectual property and proprietary rights of third parties. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, and administrative proceedings such as interferences, *inter partes* review and post grant review proceedings before the U.S. Patent and Trademark Office, or USPTO, and opposition proceedings before foreign patent offices. Numerous U.S. and foreign issued patents and pending patent applications, which are owned or controlled by third parties, including our competitors, exist in the fields in which we are pursuing products and product candidates. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our products and product candidates may be subject to claims of infringement of the patent rights of third parties.

Third parties may assert that we or our licensors are employing their proprietary technology without authorization. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment relating to our products and product candidates and, because patent applications can take many years to issue, there may be currently pending third party patent applications which may later result in issued patents, in each case that our products and product candidates, their manufacture or use may infringe or be alleged to infringe.

Parties making patent infringement claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our products or product candidates. Defense of these claims, including demonstrating non-infringement, invalidity or unenforceability of the respective patent rights in question, regardless of their merit, is time-consuming, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. For example, in order to successfully challenge the validity of any U.S. patent in federal court, we would need to overcome a presumption of validity. This is a high burden requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, and we can provide no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. We may not have sufficient resources to bring these actions to a successful conclusion. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ADSs.

In the event that a holder of any such patents seeks to enforce its patent rights against us with respect to one or more of our products or product candidates, and our defenses against the infringement of such patent rights are unsuccessful, we may be precluded from commercializing such products and product candidates, even if approved, without first obtaining a license to some or all of these patents, which may not be available on commercially reasonable terms or at all. Moreover, we may be required to pay significant fees and royalties to secure a license to the applicable patents. Such a license may only be non-exclusive, in which case our ability to stop others from using or commercializing technology and products similar or identical to ours may be limited. Furthermore, we could be liable for damages to the holders of these patents, which may be significant and could include treble damages if we are found to have willfully infringed such patents. In the event that a challenge to these patents were to be unsuccessful or we were to become subject to litigation or unable to obtain a license on commercially reasonable terms with respect to these patents, it could harm our business, financial condition, results of operations and prospects.

We are aware of third-party issued U.S. patents relating to the lentiviral vectors used in the manufacture or use of our product candidates. If these patent rights were enforced against us, we believe that we have defenses against any such action, including that these patents would not be infringed by our product candidates and/or that these patents are not valid. However, if these patents were enforced against us and defenses to such enforcement were unsuccessful, unless we obtain a license to these patents, which may not be available on commercially reasonable terms, or at all, we could be liable for damages and precluded from commercializing any products and product candidates that were ultimately held to infringe these patents, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Even in the absence of a finding of infringement, we may need to obtain licenses from third parties to advance our research or allow commercialization of our products and product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, or at all. In that event, we would be unable to further develop and commercialize our products and product candidates. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business. Any of the foregoing could materially adversely affect our business, results of operations and financial condition.

We are highly dependent on intellectual property and data licensed from third parties to develop and commercialize our products and product candidates and our development and commercialization abilities are subject, in part, to the terms and conditions of licenses granted to us by such third parties.

We are highly dependent on the intellectual property and data licensed to us by third parties that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to any of our products or product candidates. We have in-licensed one U.S. patent application and a counterpart European patent application, know-how and data from UCLA and UCL Business plc, or UCLB, relating to OTL-101 for ADA-SCID. In addition, we have in-licensed certain know-how and data from GSK and Telethon-OSR, relating to Strimvelis, OTL-103 for WAS, OTL-200 for MLD, and OTL-300 for TDBT. Any termination of these license rights could result in the loss of significant rights and could harm or prevent our ability to commercialize our products and product candidates.

Although our license rights from The Regents of the University of California, University College London GSK, and Telethon-OSR, are exclusive, they are limited to particular fields, such as ADA-SCID, MLD, WAS or TDBT, and are subject to certain retained rights. Absent an amendment or additional agreement, we may not have the right to use the in-licensed intellectual property, data, or know-how for one of our programs in another program. Furthermore, the licenses (including sublicenses) that we have or may enter into in the future may not provide rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology, products and product candidates. As a result, we may not be free to commercialize certain of our products or product candidates in fields or territories of interest to us. Furthermore, if the licenses are not exclusive in territories of interest to us, we may be unable to prevent competitors from developing and commercializing competitive products in territories included in our licenses. Licenses (including sublicenses) to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business.

In some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology that we license from third parties. Therefore, we cannot be certain that these patents and applications will be prosecuted, maintained and enforced in a manner consistent with the best interests of our business. If our licensors fail to maintain such patents, or lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our products and product candidates that are the subject of such licensed rights could be adversely affected.

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we

cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business

If we are unable to obtain and maintain patent and other intellectual property protection for our products and product candidates, or if the scope of the patent and other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products and product candidates may be adversely affected.

Our ability to compete effectively will depend, in part, on our ability to maintain the proprietary nature of our technology and manufacturing processes. We rely on manufacturing and other know-how, patents, trade secrets, license agreements and contractual provisions to establish our intellectual property rights and protect our products and product candidates. These legal means, however, afford only limited protection and may not adequately protect our rights. We currently do not own any patents or patent applications and have not in-licensed any issued patents related to any of our products or product candidates. In addition, the U.S. patent application and its counterpart European patent application we have in-licensed from The Regents of the University of California and University College London relating to OTL-101 are at a very early stage. Many of our products and product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our or our licensors' failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better financed gene therapy companies having established development, manufacturing and distribution capabilities, to make competing products or impact our ability to develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

In particular, we rely primarily on trade secrets, know-how and other unpatented technology, which are difficult to protect. Although we seek such protection in part by entering into confidentiality agreements with our vendors, employees, consultants and others who may have access to proprietary information, we cannot be certain that these agreements will not be breached, adequate remedies for any breach would be available, or our trade secrets, know-how and other unpatented proprietary technology will not otherwise become known to or be independently developed by our competitors. If we are unsuccessful in protecting our intellectual property rights, sales of our products may suffer and our ability to generate revenue could be severely impacted.

We currently do not own any issued patents related to our products and product candidates. Certain intellectual property related to Strimvelis and all of our product candidates are in-licensed from third parties but we have not in-licensed any issued patents related to Strimvelis or any of our product candidates. In certain situations and as considered appropriate, we and our licensors have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to

our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, whether the claims of any resulting patents will provide us with a competitive advantage or prevent competitors from designing around our claims to develop competing technologies in a non-infringing manner, or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection.

It is possible that defects of form in the preparation or filing of patent applications may exist, or may arise in the future, for example with respect to proper priority claims, inventorship, claim scope, or requests for patent term adjustments. If we fail to establish, maintain or protect such patents and other intellectual property rights, such rights may be reduced or eliminated. If there are material defects in the form, preparation, prosecution or enforcement of our patents or patent applications, such patents may be invalid and/or unenforceable, and such applications may never result in valid, enforceable patents. Any of these outcomes could impair our ability to prevent competition from third parties, which may have an adverse impact on our business.

Other parties, many of whom have substantially greater resources and have made significant investments in competing technologies, have developed or may develop technologies that may be related or competitive with our approach, and may have filed or may file patent applications and may have been issued or may be issued patents with claims that overlap or conflict with our patent applications, either by claiming the same compositions, formulations or methods or by claiming subject matter that could dominate our patent position. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. As a result, any patents we may obtain in the future may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our products and product candidates.

We may not be able to protect our intellectual property rights throughout the world.

Filing, prosecuting, maintaining, defending and enforcing patents on products and product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. Although our license agreement with UCLA and UCLB pertaining to OTL-101 grants us worldwide rights, and our currently in-licensed patent family relating to OTL-101 has a European patent application, there can be no assurance that we will obtain or maintain patent rights in or outside the United States under any future license agreements. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States even in jurisdictions where we and our licensors pursue patent protection. Consequently, we and our licensors may not be able to prevent third parties from practicing our inventions in all countries outside the United States, even in jurisdictions where we and our licensors pursue patent protection, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we and our licensors have not pursued and obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but

enforcement is not as strong as that in the United States. These products may compete with our products and product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights, even if obtained, in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

Issued patents covering our products and product candidates could be found invalid or unenforceable if challenged in court or in administrative proceedings. We may not be able to protect our trade secrets in court.

If one of our licensing partners or we initiate legal proceedings against a third-party to enforce a patent covering one of our products or product candidates, should such a patent issue, the defendant could counterclaim that the patent covering our product or product candidate is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, written description or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld information material to patentability from the USPTO, or made a misleading statement, during prosecution. Third parties also may raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions. An adverse determination in any of the foregoing proceedings could result in the revocation or cancellation of, or amendment to, our patents in such a way that they no longer cover our products or product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which the patent examiner and we or our licensing partners were unaware during prosecution. If a defendant or third party were to prevail on a legal assertion of invalidity or unenforceability, we could lose at least part, and perhaps all, of the patent protection on one or more of our products and product candidates. Such a loss of patent protection could have a material adverse impact on our business.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or

unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach.

In addition, our trade secrets may otherwise become known or be independently discovered by competitors. Competitors and other third parties could purchase our products and product candidates and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe, misappropriate or otherwise violate our intellectual property rights, design around our protected technology or develop their own competitive technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If our trade secrets are not adequately protected or sufficient to provide an advantage over our competitors, our competitive position could be adversely affected, as could our business. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating our trade secrets.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Certain of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management. Our licensors may face similar risks, which could have an adverse impact on intellectual property that is licensed to us.

We may be subject to claims challenging the inventorship or ownership of the patents and other intellectual property that we own or license.

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own or such assignments may not be self-executing or may be breached. Our

licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

Some intellectual property which we have in-licensed may have been discovered through government funded programs and thus may be subject to federal regulations such as "march-in" rights, certain reporting requirements, and a preference for U.S. industry. Compliance with such regulations may limit our exclusive rights, and limit our ability to contract with non-U.S. manufacturers.

Some of the intellectual property rights we have licensed, including rights licensed to us by UCLA relating to our OTL-101 product candidate for ADA-SCID, may have been generated through the use of U.S. government and California state funding and may therefore be subject to certain federal and state laws and regulations. As a result, the U.S. government may have certain rights to intellectual property embodied in our current or future products and product candidates pursuant to the Bayh-Dole Act of 1980. These U.S. government rights in certain inventions developed under a government-funded program include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (i) adequate steps have not been taken to commercialize the invention; (ii) government action is necessary to meet public health or safety needs; or (iii) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). The U.S. government also has the right to take title to these inventions if we, or the applicable licensor, fail to disclose the invention to the government and fail to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us or the applicable licensor to expend substantial resources. In addition, the U.S. government requires that products embodying the subject invention or produced through the use of the subject invention be manufactured substantially in the United States. The manufacturing preference requirement can be waived if the owner of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. manufacturers may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property. With respect to state funding, specifically funding via the California Institute of Regenerative Medicine, or CIRM, the grantee has certain obligations and the state or CIRM has certain rights. For example, the grantee has an obligation to share intellectual property, including research results, generated by CIRM-funded research, for research use in California.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe, misappropriate or otherwise violate patents, trademarks, copyrights or other intellectual property that we own or in-license. To counter infringement, misappropriation or other unauthorized use, we may be required to file claims, which can be expensive and time

consuming and divert the time and attention of our management and scientific personnel. Any claims we assert against perceived violators could provoke these parties to assert counterclaims against us alleging that we infringe, misappropriate or otherwise violate their intellectual property, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention. An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors, and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition.

Even if we establish infringement, misappropriation or another violation of our intellectual property rights, the court may decide not to grant an injunction against the offender and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our ADSs. Moreover, there can be no assurance that we will have sufficient financial or other resources to file and pursue such claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings. Any of the foregoing may have a material adverse effect on our business, financial condition, results of operations and prospects.

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our products and product candidates.

Changes in either the patent laws or the interpretation of the patent laws in the United States or other jurisdictions could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. When implemented, the Leahy-Smith Act included several significant changes to U.S. patent law that impacted how patent rights could be prosecuted, enforced and defended. In particular, the Leahy-Smith Act also included provisions that switched the United States from a "first-to-invent" system to a "first-to-file" system, allowed third-party submission of prior art to the USPTO during patent prosecution and set forth additional procedures to attack the validity of a patent by the USPTO administered post grant proceedings. Under a first-to-file system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to the patent on an invention regardless of whether another inventor had made the invention earlier. The USPTO developed new regulations and procedures governing the administration of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, only became effective on March 16, 2013. It remains unclear what, if any, impact the Leahy-Smith Act will have

on the operation of our business. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business.

The patent positions of companies engaged in the development and commercialization of biologics are particularly uncertain. Two cases involving diagnostic method claims and “gene patents” have been decided by the Supreme Court of the United States, or Supreme Court. The Supreme Court issued a decision in Mayo Collaborative Services v. Prometheus Laboratories, Inc., or Prometheus, a case involving patent claims directed to a process of measuring a metabolic product in a patient to optimize a drug dosage for the patient. According to the Supreme Court, the addition of well-understood, routine or conventional activity such as “administering” or “determining” steps was not enough to transform an otherwise patent-ineligible natural phenomenon into patent-eligible subject matter. Thereafter, the USPTO issued a guidance memo to patent examiners indicating that process claims directed to a law of nature, a natural phenomenon or a naturally occurring relation or correlation that do not include additional elements or steps that integrate the natural principle into the claimed invention such that the natural principle is practically applied and the claim amounts to significantly more than the natural principle itself should be rejected as directed to not patent-eligible subject matter. Subsequently, the Supreme Court issued its decision in Association for Molecular Pathology v. Myriad Genetics, Inc., or Myriad, a case involving patent claims held by Myriad Genetics, Inc. relating to the breast cancer susceptibility genes BRCA1 and BRCA2. Myriad held that an isolated segment of naturally occurring DNA, such as the DNA constituting the BRCA1 and BRCA2 genes, is not patent-eligible subject matter, but that complementary DNA, which is an artificial construct that may be created from RNA transcripts of genes, may be patent-eligible. Thereafter, the USPTO issued a guidance memorandum instructing USPTO examiners on the ramifications of the Prometheus and Myriad rulings and apply the Myriad ruling to natural products and principles including all naturally occurring nucleic acids.

Certain claims of our in-licensed patent applications contain, and any future patents we may obtain may contain, claims that relate to specific recombinant DNA sequences that are naturally occurring at least in part and, therefore, could be the subject of future challenges made by third parties.

We cannot assure you that our efforts to seek patent protection for one or more of our products and product candidates will not be negatively impacted by the decisions described above, rulings in other cases or changes in guidance or procedures issued by the USPTO. We cannot fully predict what impact the Supreme Court’s decisions in Prometheus and Myriad may have on the ability of life science companies to obtain or enforce patents relating to their products in the future. These decisions, the guidance issued by the USPTO and rulings in other cases or changes in USPTO guidance or procedures could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

Moreover, although the Supreme Court has held in Myriad that isolated segments of naturally occurring DNA are not patent-eligible subject matter, certain third parties could allege that activities that we may undertake infringe other gene-related patent claims, and we may deem it necessary to defend ourselves against these claims by asserting non-infringement and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement, we could be forced to pay damages or be

subjected to an injunction that would prevent us from utilizing the patented subject matter, the result of which could have a material adverse effect on our business.

If we do not obtain patent term extension and data exclusivity for our products and product candidates, our business may be materially harmed.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our products and product candidates are obtained, once the patent life has expired for a product or product candidate, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products and product candidates similar or identical to ours.

In the future, if we obtain an issued patent covering one of our present or future product candidates, depending upon the timing, duration and specifics of any FDA marketing approval of such product candidates, such patent may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent extension term of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. A patent may only be extended once and only based on a single approved product. However, we may not be granted an extension because of, for example, failure to obtain a granted patent before approval of a product candidate, failure to exercise due diligence during the testing phase or regulatory review process, failure to apply within applicable deadlines, failure to apply prior to expiration of relevant patents or otherwise our failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. In addition, we do not control the efforts of our licensors to obtain a patent term extension, and there can be no assurance that they will pursue or obtain such extensions to patents that we may license from them.

Intellectual property rights and regulatory exclusivity rights do not necessarily address all potential threats.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations, and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- the patents of others may have an adverse effect on our business;
- others, including one or more of our competitors, may reverse engineer or independently develop the know-how or data, including clinical data, that we rely on for a competitive advantage;

- others may be able to make gene therapy products that are similar to our products or product candidates but that are not covered by the claims of the patents that we license or may own or license in the future or by our other intellectual property rights;
- we, our license partners or current or future collaborators, might not have been the first to make the inventions covered by the issued patents or pending patent applications that we license or may own or license in the future;
- we, our license partners or current or future collaborators, might not have been the first to file patent applications covering certain of our or their inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing, misappropriating or otherwise violating our owned or licensed intellectual property rights;
- it is possible that our pending licensed patent applications or those that we may own or license in the future will not lead to issued patents;
- issued patents that we hold rights to or may hold rights to in the future may be held invalid or unenforceable, including as a result of legal challenges by our competitors;
- one or more of our products or product candidates may never be protected by patents;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- we or our licensors or collaborators may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

Should any of these events occur, they could significantly harm our business, financial condition, results of operations and prospects.

Risks related to this offering and ownership of our securities

We do not know whether an active, liquid and orderly trading market will develop for our ADSs or what the market price of our ADSs will be. As a result, it may be difficult for you to sell your ADSs.

This offering constitutes the initial public offering of our ADSs, and no public market has previously existed for our ADSs or ordinary shares. We intend to apply to have our ADSs listed on The Nasdaq Global Market, or Nasdaq, and we expect our ADSs to be quoted on Nasdaq, subject to completion of customary procedures in the United States. Any delay in the commencement of trading of the ADSs on Nasdaq would impair the liquidity of the market for the ADSs and make it more difficult for holders to sell the ADSs.

If the ADSs are listed and quoted on Nasdaq, there can be no assurance that an active trading market for the ADSs will develop or be sustained after this offering is completed. The initial offering price was determined by negotiations among the lead underwriters and us. Among the factors considered in determining the initial public offering price were our future prospects and

the prospects of our industry in general, our revenue, net income and certain other financial and operating information in recent periods, and the market prices of securities and certain financial and operating information of companies engaged in activities similar to ours. However, there can be no assurance that, following the completion of this offering, the ADSs will trade at a price equal to or greater than the public offering price.

The market price of our ADSs may be highly volatile, and you may not be able to resell your ADSs at or above the initial public offering price.

The market price of our ADSs following this offering is likely to be highly volatile. The stock market in general, and the market for biopharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your ADSs at or above the initial public offering price. The market price for our ADSs may be influenced by many factors, including:

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by us to maintain our existing strategic collaborations or enter into new collaborations;
- failure by us or our licensors and strategic partners to prosecute, maintain or enforce our intellectual property rights;
- changes in laws or regulations applicable to future products;
- an inability to obtain adequate product supply for our product candidates or the inability to do so at acceptable prices;
- adverse regulatory decisions;
- the introduction of new products, services or technologies by our competitors;
- failure by us to meet or exceed financial projections we may provide to the public;
- failure by us to meet or exceed the financial projections of the investment community;
- the perception of the pharmaceutical industry by the public, legislatures, regulators and the investment community;
- announcements of significant acquisitions, strategic partnerships, joint ventures or capital commitments by us, our strategic partner or our competitors;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;

- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

In addition, companies trading in the stock market in general, and Nasdaq in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. Broad market and industry factors may negatively affect the market price of our ADSs, regardless of our actual operating performance.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant securities price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

If securities or industry analysts do not publish research or publish inaccurate or unfavorable research about our business, our ADS price and trading volume could decline.

The trading market for our ADSs will likely depend in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. We do not currently have research coverage, and there can be no assurance that analysts will cover us, or provide favorable coverage. Securities or industry analysts may elect not to provide research coverage of our ADSs after this offering, and such lack of research coverage may negatively impact the market price of our ADSs. In the event we do have analyst coverage, if one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

Concentration of ownership of our ordinary shares (including ordinary shares in the form of ADSs) among our existing executive officers, directors and principal shareholders may prevent new investors from influencing significant corporate decisions.

Our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 61.6% of our ordinary shares and, upon closing of this offering, that same group will beneficially own approximately 51.7% of our outstanding ordinary shares. Depending on the level of attendance at our general meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and amendments to our Articles of Association. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that you may believe are in your best interest as one of our shareholders. Some of these persons or entities may have interests different than yours. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs are being sold in this offering and

have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

Future sales, or the possibility of future sales, of a substantial number of our securities could adversely affect the price of the shares and dilute shareholders.

If our existing shareholders sell, or indicate an intent to sell, substantial amounts of our securities in the public market, the trading price of the ADSs could decline significantly and could decline below the public offering price in this offering. Upon completion of this offering, and assuming no exercise of the underwriters' option to purchase additional ADSs, we will have 83,094,818 outstanding ordinary shares (including ordinary shares represented by the ADSs), of which approximately 69,761,485 are subject to a 180-day contractual lock-up. The representatives of the underwriters may permit us and the holders of the lock-up shares to sell shares or ADSs prior to the expiration of the lock-up agreements. See "Underwriting." After the lock-up agreements pertaining to this offering expire, and based on the number of ordinary shares (including ordinary shares represented by ADSs) outstanding upon completion of this offering, these approximately 69,761,485 additional ordinary shares will be eligible for sale in the public market, all of which shares are held by directors and certain members of our executive management and will be subject to volume limitations under Rule 144 under the Securities Act of 1933, as amended, or the Securities Act, for sales in the United States. In addition, ordinary shares subject to outstanding options under our equity incentive plans and the ordinary shares reserved for future issuance under our equity incentive plan will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. We also intend to enter into a registration rights agreement upon the closing of this offering pursuant to which we will agree under certain circumstances to file a registration statement to register the resale of the ordinary shares held by certain of our existing shareholders, as well as to cooperate in certain public offerings of such ordinary shares. In addition, we intend to register all ordinary shares that we may issue under our equity compensation plans. Once we register these ordinary shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Shares and ADSs eligible for future sale" section of this prospectus.

Holders of ADSs are not treated as holders of our ordinary shares.

By participating in this offering you will become a holder of ADSs with underlying ordinary shares in a company incorporated under English law. Holders of ADSs are not treated as holders of our ordinary shares, unless they withdraw the ordinary shares underlying their ADSs in accordance with the deposit agreement and applicable laws and regulations. The depositary is the holder of the ordinary shares underlying the ADSs. Holders of ADSs therefore do not have any rights as holders of our ordinary shares, other than the rights that they have pursuant to the deposit agreement. See "Description of American depositary shares."

Holders of ADSs may be subject to limitations on the transfer of their ADSs and the withdrawal of the underlying ordinary shares.

ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. The depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary think it is advisable to do so because of any requirement of law, government or

governmental body, or under any provision of the deposit agreement, or for any other reason, subject to the right of ADS holders to cancel their ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of your ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders' meeting or we are paying a dividend on our ordinary shares. In addition, ADS holders may not be able to cancel their ADSs and withdraw the underlying ordinary shares when they owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities. See "Description of American depositary shares."

We are entitled to amend the deposit agreement and to change the rights of ADS holders under the terms of such agreement, or to terminate the deposit agreement, without the prior consent of the ADS holders.

We are entitled to amend the deposit agreement and to change the rights of the ADS holders under the terms of such agreement, without the prior consent of the ADS holders. We and the depositary may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depositary. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depositary. In the event that the terms of an amendment are materially disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to direct the depositary to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but will have no right to any compensation whatsoever.

ADSs holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that, to the fullest extent permitted by law, holders and beneficial owners of ADSs irrevocably waive the right to a jury trial of any claim they may have against us or the depositary arising out of or relating to the ADSs or the deposit agreement.

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. However, we believe that a contractual pre-

dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs. It is advisable that you consult legal counsel regarding the jury waiver provision before entering into the deposit agreement.

If you or any other holders or beneficial owners of ADSs bring a claim against us or the depositary in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and / or the depositary. If a lawsuit is brought against us and/or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any substantive provision of the U.S. federal securities laws and the rules and regulations promulgated thereunder.

You will not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise your right to vote.

Except as described in this prospectus and the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depositary to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the depositary, upon timely notice from us, will notify ADS holders of the upcoming vote and arrange to deliver our voting materials to them. Upon our request, the depositary will mail to holders a shareholder meeting notice that contains, among other things, a statement as to the manner in which voting instructions may be given. We cannot guarantee that ADS holders will receive the voting materials in time to ensure that they can instruct the depositary to vote the ordinary shares underlying their ADSs. A shareholder is only entitled to participate in, and vote at, the meeting of shareholders, provided that it holds our ordinary shares as of the record date set for such meeting and otherwise complies with our Articles of Association. In addition, the depositary's liability to ADS holders for failing to execute voting instructions or for the manner of executing voting instructions is limited by the deposit agreement. As a result, holders of ADSs may not be able to exercise their right to give voting instructions or to vote in person or by proxy and they may not have any recourse against the depositary or us if their ordinary shares are not voted as they have requested or if their shares cannot be voted.

You may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

The depositary for the ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses. You will receive these distributions in proportion to the number of our ordinary shares your ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that you may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have an adverse effect on the value of your ADSs.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

Under current English law, a company's accumulated realized profits must exceed its accumulated realized losses (on a non-consolidated basis) before dividends can be declared and paid. Therefore, we must have distributable profits before declaring and paying a dividend. We have not paid dividends in the past on our ordinary shares. We intend to retain earnings, if any, for use in our business and do not anticipate paying any cash dividends in the foreseeable future. As a result, capital appreciation, if any, on our ADSs will be your sole source of gains for the foreseeable future, and you will suffer a loss on your investment if you are unable to sell your ADSs at or above the initial public offering price. Investors seeking cash dividends should not purchase our ADSs in this offering.

If you purchase our ADSs in this offering, you will incur immediate and substantial dilution in the book value of your shares.

Investors purchasing ADSs in this offering will pay a price per share that substantially exceeds the pro forma book value per share of our tangible assets after subtracting our liabilities. As a result, investors purchasing ADSs in this offering will incur immediate dilution of $10.85 per ADS, based on the initial public offering price of $15.00 per ADS, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and our pro forma as adjusted net tangible book value as of June 30, 2018. Further, investors purchasing ADSs in this offering will contribute approximately 41.2% of the total amount invested by shareholders since our inception, but will own only approximately 16.0% of the ordinary shares outstanding. For information on how the foregoing amounts were calculated, see "Dilution."

A significant portion of our total outstanding ordinary shares are restricted from immediate resale but may be sold into the market in the near future, which could cause the market price of our ADSs to drop significantly.

Sales of a substantial number of our ADSs in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. After this offering, assuming no exercise of the underwriters' option to purchase additional ADSs, we will have outstanding 83,094,818 ordinary shares based on the number of ordinary shares outstanding as of September 30, 2018, (or 85,094,817 ordinary shares if the underwriters exercise their option to

purchase additional ADSs in full). This includes the 13,333,333 ADSs that we are selling in this offering (or 15,333,332 ADSs if the underwriters exercise their option to purchase additional ADSs in full), which may be resold in the public market immediately without restriction, unless purchased by our affiliates. The remaining 69,761,485 shares currently are restricted as a result of securities laws or lock-up agreements but will be able to be sold after the offering as described in the "Shares and ADSs eligible for future sale" and "Underwriting" sections of this prospectus. Moreover, after this offering, holders of an aggregate of approximately 60,168,900 ordinary shares will have rights, subject to certain conditions, to require us to file registration statements covering their ordinary shares or to include their ordinary shares in registration statements that we may file for ourselves or other shareholders. In addition, 10,135,454 ordinary shares reserved for issuance upon the exercise of existing options outstanding as of September 30, 2018 under our current equity incentive plan will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. We intend to register all ordinary shares that we may issue under our equity compensation plans. Once we register these ordinary shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Underwriting" section of this prospectus.

In addition, J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC may, in their sole discretion, release all or some portion of the ordinary shares subject to lock-up agreements at any time and for any reason. Sales of a substantial number of such ordinary shares upon expiration of the lock-up agreements, the perception that such sales may occur, or early release of these agreements, could cause our market price to fall or make it more difficult for you to sell your ADSs at a time and price that you deem appropriate.

We have broad discretion in the use of the net proceeds from this offering and may not use them effectively.

Our management will have broad discretion in the application of the net proceeds from this offering, including for any of the purposes described in the section entitled "Use of proceeds," and you will not have the opportunity as part of your investment decision to assess whether the net proceeds are being used appropriately. Because of the number and variability of factors that will determine our use of the net proceeds from this offering, their ultimate use may vary substantially from their currently intended use. The failure by our management to apply these funds effectively could harm our business. Pending their use, we may invest the net proceeds from this offering in short-term, investment-grade, interest-bearing securities. These investments may not yield a favorable return to our shareholders.

Claims of U.S. civil liabilities may not be enforceable against us.

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and all or a substantial portion of our assets and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

The United States and the United Kingdom do not currently have a treaty providing for recognition and enforcement of judgments (other than arbitration awards) in civil and

commercial matters. Consequently, a final judgment for payment given by a court in the United States, whether or not predicated solely upon U.S. securities laws, would not automatically be recognized or enforceable in the United Kingdom. In addition, uncertainty exists as to whether U.K. courts would entertain original actions brought in the United Kingdom against us or our directors or senior management predicated upon the securities laws of the United States or any state in the United States. Any final and conclusive monetary judgment for a definite sum obtained against us in U.S. courts would be treated by the courts of the United Kingdom as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that certain requirements are met. Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the U.S. securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision. If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement.

As a result, U.S. investors may not be able to enforce against us or our senior management, board of directors or certain experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

As a foreign private issuer, we are exempt from a number of rules under the U.S. securities laws and are permitted to file less information with the SEC than U.S. public companies.

We are a “foreign private issuer,” as defined in the SEC rules and regulations and, consequently, we are not subject to all of the disclosure requirements applicable to companies organized within the United States. For example, we are exempt from certain rules under the Exchange Act that regulate disclosure obligations and procedural requirements related to the solicitation of proxies, consents or authorizations applicable to a security registered under the Exchange Act. In addition, our officers and directors are exempt from the reporting and “short-swing” profit recovery provisions of Section 16 of the Exchange Act and related rules with respect to their purchases and sales of our securities. Moreover, we are not required to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. public companies. Accordingly, there may be less publicly available information concerning our company than there is for U.S. public companies.

As a foreign private issuer, we will file an annual report on Form 20-F within four months of the close of each fiscal year ended December 31 and reports on Form 6-K relating to certain material events promptly after we publicly announce these events. However, because of the above exemptions for foreign private issuers, our shareholders will not be afforded the same protections or information generally available to investors holding shares in public companies organized in the United States.

While we are a foreign private issuer, we are not subject to certain Nasdaq corporate governance rules applicable to U.S. listed companies.

We are entitled to rely on a provision in Nasdaq’s corporate governance rules that allows us to follow English corporate law and the Companies Act with regard to certain aspects of corporate governance. This allows us to follow certain corporate governance practices that differ in significant respects from the corporate governance requirements applicable to U.S. companies listed on Nasdaq.

For example, we are exempt from Nasdaq regulations that require a listed U.S. company to (i) have a majority of the board of directors consist of independent directors, (ii) require non-management directors to meet on a regular basis without management present and (iii) promptly disclose any waivers of the code for directors or executive officers that should address certain specified items.

In accordance with our Nasdaq listing, our audit committee is required to comply with the provisions of Section 301 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and Rule 10A-3 of the Exchange Act, both of which are also applicable to Nasdaq -listed U.S. companies. Because we are a foreign private issuer, however, our audit committee is not subject to additional Nasdaq requirements applicable to listed U.S. companies, including an affirmative determination that all members of the audit committee are "independent," using more stringent criteria than those applicable to us as a foreign private issuer. Furthermore, Nasdaq's corporate governance rules require listed U.S. companies to, among other things, seek shareholder approval for the implementation of certain equity compensation plans and issuances of ordinary shares, which we are not required to follow as a foreign private issuer.

We may lose our foreign private issuer status which would then require us to comply with the Exchange Act's domestic reporting regime and cause us to incur significant legal, accounting and other expenses.

As a foreign private issuer, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. We may no longer be a foreign private issuer as early as June 30, 2019 (the end of our second fiscal quarter in the fiscal year after completion of this offering), which would require us to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers as of January 1, 2020. In order to maintain our current status as a foreign private issuer, either (a) a majority of our securities must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors cannot be U.S. citizens or residents, (ii) more than 50% of our assets must be located outside the United States and (iii) our business must be administered principally outside the United States. If we lose our status as a foreign private issuer, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We may also be required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as a foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and is likely to make some activities highly time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our ADSs less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart our Business Startups Act of 2012, or the JOBS Act. We will remain an EGC until the earliest of: (i) the last day of the fiscal year in which we have total annual gross revenues of $1.07 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the completion of this offering; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC, which means the first day of the year following the first year in which the market value of our ADSs that are held by non-affiliates exceeds $700 million as of June 30. For so long as we remain an EGC, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, or Section 404;
- not being required to comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- being permitted to provide only two years of audited financial statements in this initial registration statement, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's discussion and analysis of financial condition and results of operations" disclosure;
- reduced disclosure obligations regarding executive compensation; and
- an exemption from the requirement to seek nonbinding advisory votes on executive compensation or golden parachute arrangements.

We may choose to take advantage of some, but not all, of the available exemptions. We have taken advantage of reduced reporting burdens in this prospectus. In particular, we have not included all of the executive compensation information that would be required if we were not an EGC. We cannot predict whether investors will find our ADSs less attractive if we rely on certain or all of these exemptions. If some investors find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and our ADS price may be more volatile.

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We will incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management will be required to devote substantial time to new compliance initiatives.

As a U.S. public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In

addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

Pursuant to Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. To achieve compliance with Section 404 within the prescribed period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. Despite our efforts, there is a risk we will not be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

If we fail to maintain an effective system of internal control over financial reporting, we may not be able to accurately report our financial results or prevent fraud. As a result, shareholders could lose confidence in our financial and other public reporting, which would harm our business and the trading price of our ADSs.

Effective internal controls over financial reporting are necessary for us to provide reliable financial reports and, together with adequate disclosure controls and procedures, are designed to prevent fraud. Any failure to implement required new or improved controls, or difficulties encountered in their implementation could cause us to fail to meet our reporting obligations. In addition, any testing by us conducted in connection with Section 404, or any subsequent testing by our independent registered public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses or that may require prospective or retroactive changes to our financial statements or identify other areas for further attention or improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

Our management will be required to assess the effectiveness of these controls annually. However, for as long as we are an EGC, our independent registered public accounting firm will not be required to attest to the effectiveness of our internal controls over financial reporting pursuant to Section 404. We could be an EGC for up to five years. An independent assessment of the effectiveness of our internal controls over financial reporting could detect problems that our management’s assessment might not. Undetected material weaknesses in our internal controls over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

We have identified material weaknesses in our internal control over financial reporting. If we are unable to remedy these material weaknesses, or if we fail to establish and maintain effective internal controls, we may be unable to produce timely and accurate financial statements, and we may conclude that our internal control over financial reporting is not effective, which could adversely impact our investors' confidence and our ADS price.

We have historically been a private limited company, and as such, have not historically been subject to the reporting requirements of Section 404 or an audit performed in accordance with auditing standards issued by the PCAOB. However, in connection with the preparation of our consolidated financial statements for the years ended December 31, 2016 and 2017, we identified material weaknesses in our internal control over financial reporting attributable to our lack of experienced financial reporting and accounting personnel familiar with U.S. GAAP during these periods. Specifically, the findings relates to our internal control infrastructure as of December 31, 2016 and 2017 and June 30, 2018 where we did not design or implement sufficient processes, controls and other review procedures to evaluate (i) the recognition and accrual of research and development related expenses and reimbursements for periods ended December 31, 2016 and 2017 and (ii) the recognition of assets and liabilities contingent on future events for the six-month period ending June 30, 2018. As a result, there were adjustments required in connection with closing our books and records and preparing our 2016 and 2017 financial statements, and a restatement of our condensed consolidated financial statements as of and for the six months ended June 30, 2018.

We are implementing measures designed to improve our internal control over financial reporting to remediate these material weaknesses, including formalizing our processes and internal control documentation and strengthening supervisory reviews by our financial management; hiring additional qualified accounting and finance personnel and engaging financial consultants to enable the implementation of internal control over financial reporting and segregating duties amongst accounting and finance personnel; and planning to implement certain accounting systems to automate manual processes.

We expect to incur additional costs to remediate these control deficiencies, though there can be no assurance that our efforts will be successful or avoid potential future material weaknesses. If we are unable to successfully remediate our existing or any future material weaknesses in our internal control over financial reporting, or if we identify any additional material weaknesses, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose confidence in our financial reporting, and our ADS price may decline as a result. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

Upon completion of this offering, we will become subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or

mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law the TCJA, which makes significant changes to the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation and other changes that may impact our operations, in particular the operations of our wholly-owned U.S. subsidiary, Orchard Therapeutics North America. We continue to examine the impact the TCJA may have on our business, though the effect of the TCJA on our business is uncertain. We urge investors to consult with their legal and tax advisers regarding the implications of the TCJA on an investment in our ordinary shares or ADSs.

If we are a controlled foreign corporation, there could be adverse U.S. federal income tax consequences to certain U.S. holders

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of the CFC's "Subpart F income" and investment of earnings in U.S. property, even if the CFC has made no distributions to its shareholders. Subpart F income generally includes dividends, interest, rents, royalties, "global intangible low-taxed income," gains from the sale of securities and income from certain transactions with related parties. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in a CFC may be required to classify a portion of such gain as dividend income rather than capital gain. A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of the total combined voting power of all classes of stock entitled to vote of such corporation. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain.

We believe that we were not a CFC in the 2017 taxable year, though we have not made a determination regarding our CFC status in the current taxable year, and we may become a CFC in a subsequent taxable year. U.S. Holders (as defined below under "Material income tax considerations—Material U.S. federal income tax considerations for U.S. holders") should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a passive foreign investment company, or PFIC (as discussed below), we generally will not be treated as a PFIC with respect to those U.S. Holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

If we are a PFIC there could be adverse U.S. federal income tax consequences to U.S. holders.

Under the Code, we will be a PFIC, for any taxable year in which (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of

these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. Holder holds our shares, the U.S. Holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

We do not believe that we were a PFIC in the 2017 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering, including this offering.

In certain circumstances, a U.S. Holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a “qualified electing fund,” or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute “marketable” securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. However, a U.S. Holder may make a QEF election with respect to our ordinary shares or ADSs only if we agree to furnish such U.S. Holder annually with required information, and we have not determined if we intend to prepare or provide the information that would enable U.S. Holders to make a QEF election. However, a U.S. Holder would be able to make a mark-to-market election with respect to our ordinary shares or ADSs as long as those shares or ADSs constitute marketable securities under the Code.

For further discussion of the PFIC rules and the adverse U.S. federal income tax consequences in the event we are classified as a PFIC, see the section of this prospectus entitled “Material income tax considerations—Material U.S. federal income considerations for U.S. holders.”

We may be unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable U.K. tax legislation.

As a U.K. incorporated and tax resident entity, we are subject to U.K. corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any U.K. corporation tax. As of December 31, 2017, we had cumulative carryforward tax losses of $48.4 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation

to U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

As a company that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program, or SME Program, and the Research and Development Expenditure program, or RDEC Program. Where available, we may be able to surrender the trading losses that arise from our qualifying research and development activities for cash or carried forward for potential offset against future profits (subject to relevant restrictions). The majority of our pipeline research, clinical trials management and manufacturing development activities are eligible for inclusion within these tax credit cash rebate claims. We may not be able to continue to claim payable research and development tax credits in the future when we become a public company because we may no longer qualify as a small or medium-sized company.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the "patent box" regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

The Company may be liable for stamp duty in connection with the Corporate Reorganization.

In connection with the Corporate Reorganization, there will be a transfer of the entire issued share capital of Orchard Therapeutics Limited to the Company prior to the completion of this offering. The Company will make an application to HM Revenue & Customs for such transfer to be adjudicated as not chargeable to stamp duty by virtue of section 77 of the Finance Act 1986. While it is expected that all of the conditions of section 77 of the Finance Act 1986 can be satisfied and relief should be available, if such relief is not forthcoming the Company will be required to pay 0.5% stamp duty of the value of the consideration given for that transfer, which is expected to be, broadly, 0.5% of the value of the Orchard Therapeutics Limited share capital transferred.

Shareholder protections found in provisions under the U.K. City Code on Takeovers and Mergers, or the Takeover Code, will not apply if our place of management and control is considered to change to outside the United Kingdom.

Prior to the consummation of this offering, we will re-register as a public limited company incorporated in England and Wales. Our place of central management and control is currently in the United Kingdom. Accordingly, we are currently subject to the Takeover Code and, as a result, our shareholders are entitled to the benefit of certain takeover offer protections provided under the Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted. If, at the time of a takeover offer, the Panel on Takeovers and Mergers determines that we do not have our place of central management and control in the

United Kingdom, then the Takeover Code would not apply to us and our shareholders would not be entitled to the benefit of the various protections that the Takeover Code affords. In particular, we would not be subject to the rules regarding mandatory takeover bids. The following is a brief summary of some of the most important rules of the Takeover Code:

- When a person or group (a) acquires interests in shares carrying 30% or more of the voting rights of a company (which percentage is treated by the Takeover Code as the level at which effective control is obtained) or (b) increases the aggregate percentage interest they have when they are already interested in not less than 30% and not more than 50%, they must make a cash offer to all other shareholders at the highest price paid by them in the 12 months before the offer was announced.
- When interests in shares carrying 10% or more of the voting rights of a class have been acquired by an offeror (i.e., a bidder) in the offer period (i.e. before the shares subject to the offer have been acquired) and the previous 12 months, the offer must include a cash alternative for all shareholders of that class at the highest price paid by the offeror in that period. Further, if an offeror acquires for cash any interest in shares during the offer period, a cash alternative must be made available at a price at least equal to the price paid for such shares.
- If the offeror acquires an interest in shares in an offeree company (i.e., a target) at a price higher than the value of the offer, the offer must be increased accordingly.
- The offeree company must appoint a competent independent adviser whose advice on the financial terms of the offer must be made known to all the shareholders, together with the opinion of the board of directors of the offeree company.
- Favorable deals for selected shareholders are not permitted, except in certain circumstances where independent shareholder approval is given and the arrangements are regarded as fair and reasonable in the opinion of the financial adviser to the offeree.
- All shareholders must be given the same information.
- Those issuing takeover circulars must include statements taking responsibility for the contents thereof.
- Profit forecasts, quantified financial benefits statements and asset valuations must be made to specified standards and must be reported on by professional advisers.
- Misleading, inaccurate or unsubstantiated statements made in documents or to the media must be publicly corrected immediately.
- Actions during the course of an offer by the offeree company, which might frustrate the offer are generally prohibited unless shareholders approve these plans. Frustrating actions would include, for example, lengthening the notice period for directors under their service contract or agreeing to sell off material parts of the target group.
- Stringent requirements are laid down for the disclosure of dealings in relevant securities during an offer, including the prompt disclosure of positions and dealing in relevant securities by the parties to an offer and any person who is interested (directly or indirectly) in 1% or more of any class of relevant securities.
- Employees of both the offeror and the offeree company and the trustees of the offeree company’s pension scheme must be informed about an offer. In addition, the offeree

company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

The rights of our shareholders may differ from the rights typically offered to shareholders of a U.S. corporation.

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act 2006, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations. See "Description of share capital and articles of association—Differences in corporate law" in this prospectus for a description of the principal differences between the provisions of the Companies Act applicable to us and, for example, the Delaware General Corporation Law relating to stockholders' rights and protections.

The principal differences include the following:

- Under English law and our Articles of Association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings.
- Under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. You should be aware, however, that the voting rights of ADSs are also governed by the provisions of a deposit agreement with our depositary bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of Association. This may make it more difficult for us to complete corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other significant transactions.
- In the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, for so long as we continue to be subject to the UK Takeover Code, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a "squeeze out" to obtain 100% control of us. Accordingly, acceptances of 90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting for approval.

- Under English law and our Articles of Association, shareholders and other persons whom we know or have reasonable cause to believe are, or have been, interested in our shares may be required to disclose information regarding their interests in our shares upon our request, and the failure to provide the required information could result in the loss or restriction of rights attaching to the shares, including prohibitions on certain transfers of the shares, withholding of dividends and loss of voting rights. Comparable provisions generally do not exist under U.S. law.
- The quorum requirement for a shareholders' meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder which is a corporation, represented by a duly authorized officer. Under U.S. law, a majority of the shares eligible to vote must generally be present (in person or by proxy) at a shareholders' meeting in order to constitute a quorum. The minimum number of shares required for a quorum can be reduced pursuant to a provision in a company's certificate of incorporation or bylaws, but typically not below one-third of the shares entitled to vote at the meeting.

Special note regarding forward-looking statements

This prospectus contains express or implied forward-looking statements that involve substantial risks and uncertainties. In some cases, you can identify forward-looking statements by the words “may,” “might,” “will,” “could,” “would,” “should,” “expect,” “intend,” “plan,” “objective,” “anticipate,” “believe,” “estimate,” “predict,” “potential,” “continue,” “ongoing,” or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The forward-looking statements and opinions contained in this prospectus are based upon information available to our management as of the date of this prospectus and, while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. Forward-looking statements contained in this prospectus include, but are not limited to, statements about:

- the timing, progress and results of clinical trials and preclinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work, the period during which the results of the trials will become available and our research and development programs;
- the timing, scope or likelihood of regulatory submissions, filings, and approvals;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the size of the patient populations for our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial product, product candidates and technology;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of our commercial product and product candidates, if approved;
- the scalability and commercial viability of our manufacturing methods and processes, including our plans to develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- the rate and degree of market acceptance and clinical utility of our commercial product and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our commercial product and product candidates;

- developments and projections relating to our competitors and our industry;
- our expectations related to the use of proceeds from this offering;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our expectations regarding the time during which we will be an emerging growth company under the JOBS Act; and
- other risks and uncertainties, including those listed under the caption “Risk factors.”

You should refer to the section titled “Risk factors” for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this prospectus will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

You should read this prospectus and the documents that we reference in this prospectus and have filed as exhibits to the registration statement of which this prospectus is a part completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

Exchange rate information

Our headquarters are located in the United Kingdom, and we maintain our books and records in pounds sterling. Fluctuations in the exchange rate between the pounds sterling and the U.S. dollar will affect the U.S. dollar amounts received by owners of our ADSs on conversion of dividends, if any, paid in pounds sterling on the ordinary shares and will affect the U.S. dollar price of our ADSs on Nasdaq. The table below presents the period end, average, high and low exchange rates of U.S. dollars per pound sterling for the periods indicated. Average rates are computed by using the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar on the last business day of each month during the relevant year indicated or each business day during the relevant month indicated. The rates set forth below are provided solely for your convenience and may differ from the actual rates used in the preparation of our consolidated financial statements included in this prospectus and other financial data appearing in this prospectus.

Year ended December 31:	Period-end(1)	Average for period(2)	Low	High
		($ per £1.00)		
2013	1.6574	1.5642	1.4837	1.6574
2014	1.5578	1.6484	1.5517	1.7165
2015	1.4746	1.5284	1.4648	1.5882
2016	1.2337	1.3555	1.2155	1.4800
2017	1.3529	1.2890	1.2118	1.3578
2018 (through October 12, 2018)	1.3154	1.3499	1.2685	1.4332

(1) In the event that the period end fell on a day for which data are not available, the exchange rate on the prior most recent business day is given.

(2) The average of the noon buying rate for pounds sterling on the last day of each full month during the relevant year or each business day during the relevant month indicated.

	Low	High
	($ per £1.00)	
Month Ended:		
January 2018	1.3513	1.4264
February 2018	1.3794	1.4247
March 2018	1.3755	1.4236
April 2018	1.3751	1.4332
May 2018	1.3258	1.3611
June 2018	1.3095	1.3429
July 2018	1.2987	1.3266
August 2018	1.2685	1.3120
September 2018	1.2833	1.3237
October 2018 (through October 12, 2018)	1.2984	1.3206

Unless otherwise indicated, certain pounds sterling amounts contained in this prospectus have been translated into U.S. dollars at the rate in effect at December 29, 2017, the last business day of the year ended December 31, 2017, of $1.3529 to £1.00.

On October 12, 2018, the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar was £1.00 to $1.3154.

Use of proceeds

We estimate that the net proceeds to us in this offering will be $181.9 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, based on an assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus. If the underwriters exercise their option to purchase additional ADSs in full, we estimate that the net proceeds to us from this offering will be $209.75 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per ADS would increase (decrease) the net proceeds to us from this offering by $12.4 million, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. An increase (decrease) of 1,000,000 in the number of ADSs we are offering would increase (decrease) the net proceeds to us from this offering by $14.0 million, assuming the assumed initial public offering price remains the same.

We expect to use the net proceeds from this offering, together with our existing cash, as follows:

- approximately $65.8 million to fund the ongoing development of our product candidates, including completing registrational trials and submitting for regulatory approvals in the United States and Europe for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, establishing clinical proof of concept for OTL-102, further progressing OTL-300, OTL-201 and OTL-202 and advancing our preclinical programs;
- approximately $17.8 million to fund the ongoing commercialization of Strimvelis in the European Union and to expand our marketing and sales infrastructure in key markets, including the United States and Europe, in preparation for the potential commercial approval of OTL-101, OTL-200 and OTL-103;
- approximately $84.5 million to fund the design, construction, and operation of our own manufacturing facility, including the necessary laboratory and manufacturing equipment, to support our long-term capacity needs for our product pipeline; and
- the remainder to fund ongoing business development activities, general and administrative expenses, working capital and other general corporate purposes.

This expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. We may also use a portion of the net proceeds to in-license, acquire, or invest in additional businesses, technologies, products or assets. We cannot predict with certainty all of the particular uses for the net proceeds to be received upon the closing of this offering or the amounts that we will actually spend on the uses set forth above. Predicting the cost necessary to commercialize approved products and develop product candidates can be difficult and the amounts and timing of our actual expenditures may vary significantly depending on numerous factors, including the progress of our development, our plans to develop our in-house drug product and vector manufacturing capabilities, the status of and results from clinical trials, any collaborations that we may enter into with third parties for our product candidates and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Based on our planned use of the net proceeds from this offering and our existing cash, we estimate that such funds will be sufficient to fund our operations and capital expenditure requirements into the second half of 2020. We have based this estimate on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we currently expect.

Pending our use of proceeds from this offering, we plan to invest these net proceeds in a variety of capital preservation instruments, including short-term, interest bearing obligations and investment-grade instruments.

Dividend policy

We have never declared or paid any cash dividend, and we do not anticipate declaring or paying any cash dividends in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. See the section titled “Risk factors—Risks related to this offering and ownership of our securities—Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.”

Under English law, among other things, we may only pay dividends if we have sufficient distributable reserves (on a non-consolidated basis), which are our accumulated realized profits that have not been previously distributed or capitalized less our accumulated realized losses, so far as such losses have not been previously written off in a reduction or reorganization of capital.

Corporate reorganization

Orchard Rx Limited is a private company with limited liability incorporated in England and Wales in August 2018, for the purpose of consummating the corporate reorganization described herein. Pursuant to the terms of a corporate reorganization to be effected prior to the completion of this offering, all shareholders of Orchard Therapeutics Limited will exchange each of the shares held by them for the same number and class of newly issued shares of Orchard Rx Limited and, as a result, Orchard Therapeutics Limited will become a wholly owned subsidiary of Orchard Rx Limited. Subsequently, we intend to re-register Orchard Rx Limited as a public limited company and rename it as Orchard Therapeutics plc. Prior to the re-registration of Orchard Rx Limited as a public company, Orchard Therapeutics Limited will change its name to Orchard Therapeutics (Europe) Limited. Therefore, investors in this offering will only acquire, and this prospectus only describes the offering of, ADSs representing shares of Orchard Therapeutics plc. We refer to the reorganization, pursuant to which Orchard Rx Limited will acquire all of the interests in Orchard Therapeutics Limited in exchange for the same number and class of newly issued shares of Orchard Rx Limited, and the subsequent re-registration of Orchard Rx Limited as a public limited company to be re-named Orchard Therapeutics plc, as our “corporate reorganization.”

Off-Balance Sheet Arrangements

We are not party to any off-balance sheet transactions. We have no guarantees or obligations other than those which arise out of normal business operations.

The corporate reorganization will take place in several steps, all of which will be completed prior to the completion of this offering.

Exchange of Orchard Therapeutics Limited shares for Orchard Rx Limited shares

Prior to this offering, the share capital of Orchard Therapeutics Limited was divided into 11,986,245 ordinary shares; 21,000,000 Series A convertible preferred shares; 21,198,154 Series B convertible preferred shares; 15,563,230 Series B-2 convertible preferred shares; and 17,421,600 Series C convertible preferred shares. Prior to the effectiveness of the registration statement of which this prospectus forms a part, the shareholders of Orchard Therapeutics Limited exchanged each of these classes of shares of Orchard Therapeutics Limited for the same number and class of shares in Orchard Rx Limited. As a result, Orchard Rx Limited became the sole shareholder of Orchard Therapeutics Limited. Following the share exchange, holders of options over shares in Orchard Therapeutics Limited will exchange their options for options over shares in Orchard Rx Limited.

Reduction of Capital of Orchard Rx Limited

Following the share exchange, Orchard Rx Limited will reduce its issued share capital pursuant to Part 17 of the Companies Act 2006 by reducing the nominal value of each issued share from £7.00 to £0.08003. The amount of the reduction of share capital will be credited to Orchard Rx Limited’s reserves available for distribution.

Reorganization of Orchard Rx Limited and re-registration of Orchard Rx Limited as Orchard Therapeutics plc

Following the steps described above and prior to the completion of this offering, Orchard Rx Limited will re-register as a public limited company and change its name to Orchard Therapeutics

plc. Such re-registration will require the passing of special resolutions by the current shareholders of Orchard Rx Limited to approve the re-registration as a public limited company, the name change to Orchard Therapeutics plc and the adoption of a new articles of association for Orchard Therapeutics plc. Prior to the re-registration of Orchard Rx Limited as a public limited company, Orchard Therapeutics Limited will change its name to Orchard Therapeutics (Europe) Limited.

Reorganisation of Separate Classes of Shares of Orchard Therapeutics plc into a Single Class of Ordinary Shares and a Single Class of Deferred Shares

Conditional upon and effective immediately prior to the completion of this offering, each class of shares in the issued share capital of Orchard Therapeutics plc will be organised into a single class of ordinary share and a single class of deferred share as follows:

- every Series A preferred share will be consolidated into 0.8003 Series A preferred shares;
- every Series B preferred share will be consolidated into 0.8003 Series B preferred shares;
- every Series B-2 preferred share will be consolidated into 0.8003 Series B-2 preferred shares;
- every Series C preferred share will be consolidated into 0.8003 Series C preferred shares;
- every ordinary share will be consolidated into 0.8003 ordinary shares; and
- following completion of the above steps, each share shall be re-designated as an ordinary share on a one-for-one basis.

Fractional entitlements to shares resulting from the above consolidation shall be consolidated into a single deferred share.

Certain further resolutions will be passed by the shareholders of Orchard Therapeutics plc prior to the completion of this offering, details of which are set out in the section titled “Description of share capital and articles of association.”

As a result of the above-described actions, upon consummation of the corporate reorganization and prior to the completion of this offering, the current shareholders of Orchard Therapeutics Limited will hold an aggregate of 69,761,485 ordinary shares of Orchard Therapeutics plc.

Capitalization

The following table sets forth our cash and capitalization of Orchard Therapeutics Limited as of June 30, 2018 on:

- an actual basis, not reflecting the 1-for-0.8003 reverse share split to be effected prior to completion of this offering; and
- a pro forma basis to give effect to:
  - our sale of 13,942,474 shares of Series C convertible preferred shares in August 2018 at a price of $10.76 per share for net proceeds of $148.0 million and conversion into an aggregate of 13,942,474 ordinary shares upon closing of this offering which resulted in an increase of cash and additional paid-in capital of $148.0 million;
  - a 1-for-0.8003 reverse share split to be effected prior to completion of this offering;
  - the conversion of all outstanding convertible preferred shares as of June 30, 2018 into an aggregate of 46,226,426 ordinary shares upon the closing of this offering which resulted in a reduction of convertible preferred shares of $229.7 million and increase of ordinary shares of $1,000 and additional paid-in capital of $229.7 million; and
- on a pro forma as adjusted basis giving effect to the pro forma adjustments set forth above and to give further effect to the sale of 13,333,333 ADSs in this offering.

The pro forma as adjusted calculations assume an initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

You should read this information together with our audited consolidated financial statements and related notes appearing elsewhere in this prospectus and the information set forth under the sections titled “Selected consolidated financial data,” “Exchange rate information,” “Use of proceeds” and “Management’s discussion and analysis of financial condition and results of operations.”

	As of June 30, 2018 (in thousands, except share and per share data)		
	Actual (as restated)	Pro forma	Pro forma as adjusted(1)
Cash	$ 48,762	$ 196,742	$ 378,592
Shareholders’ equity:			
Convertible preferred shares, £0.00001 par value; 46,226,426 shares authorized, 46,226,426 shares issued and outstanding as of June 30, 2018; no shares authorized, issued and outstanding, pro forma; no shares authorized, issued and outstanding, pro forma as adjusted	229,709	—	—
Ordinary shares, £0.00001 par value; 11,793,356 shares issued and outstanding, actual; 69,761,485 shares issued and outstanding, pro forma; 83,094,818 shares issued and outstanding, pro forma as adjusted	—	1	8,680
Additional paid-in capital	9,885	387,572	560,743
Accumulated other comprehensive (loss) income	6,097	6,097	6,097
Accumulated deficit	(230,945)	(230,945)	(230,945)
Total shareholders’ equity	14,746	162,725	344,575
Total capitalization	$ 14,746	$ 162,725	$ 344,575

(1) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 13,333,333 shares of our ordinary shares in this offering at an assumed initial public offering price of $15.00 per share, which is the midpoint of the price range set forth on the cover page of this prospectus, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

The pro forma as adjusted information discussed above is illustrative only and will change based on the actual initial public offering price and other terms of this offering determined at pricing. Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, working capital, total shareholders’ equity and total capitalization by $12.4 million, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. An increase (decrease) of 1,000,000 in the number of ADSs offered by us, as set forth on the cover page of this prospectus, would increase (decrease) the pro forma as adjusted amount of each of cash, total shareholders’ equity and total capitalization by $14.0 million, assuming no change in the initial public offering price per ADS.

The number of ordinary shares outstanding in the table above does not include:

- 10,135,454 ordinary shares issuable upon the exercise of share options outstanding as of September 30, 2018, with a weighted average exercise price of $2.79 per share;
- 14,191 ordinary shares reserved for issuance under our 2016 Employee Share Option Plan, or the 2016 Plan, as of September 30, 2018, which shares will no longer be reserved following this offering;
- 4,254,741 ordinary shares reserved for future issuance under our 2018 Share Options and Incentive Plan, or 2018 Plan, which will become effective upon the effectiveness of the

registration statement of which this prospectus forms a part, as well as any automatic increases in the number of ordinary shares reserved for future issuance under the 2018 Plan; or

- 850,948 ordinary shares reserved for future issuance under our 2018 Employee Share Purchase Plan, or the ESPP, which will become effective upon the effectiveness of the registration statement of which this prospectus forms a part, as well as any automatic increases in the number of ordinary shares reserved for future issuances under the ESPP.

Dilution

If you invest in our ADSs in this offering, your interest will be immediately diluted to the extent of the difference between the initial public offering price per ADS in this offering and the pro forma as adjusted net tangible book value per ADS after this offering. Dilution results from the fact that the initial public offering price per ADS is substantially in excess of the net tangible book value per ADS. As of June 30, 2018, we had a historical net tangible book value of $14.7 million, or $1.56 per ordinary share (equivalent to $1.56 per ADS). Our net tangible book value per share represents total tangible assets less total liabilities, divided by the number of ordinary shares outstanding on June 30, 2018.

After giving effect to (i) the issuances of ordinary shares since June 30, 2018 and our Series C issuances in August 2018, (ii) our corporate reorganization (including a 1-for-0.8003 reverse stock split) and (iii) the sale of 13,333,333 ADSs in this offering at an assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, and after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value at June 30, 2018 would have been $4.15 per ordinary share, or $4.15 per ADS. This represents an immediate increase in pro forma as adjusted net tangible book value, after considering all issuances subsequent to June 30, 2018, of $1.82 per ADS to new investors and immediate dilution of $10.85 per ADS to new investors. The following table illustrates this dilution to new investors purchasing ADSs in this offering:

Assumed initial public offering price per ADS		$15.00
Historical net tangible book value per ADS as of June 30, 2018	$ 1.56	
Effect of ordinary share issuances since June 30, 2018(1)	(0.02)	
Effect attributable to issuance of Series C and conversion to ordinary shares(2)	5.37	
Effect attributable to our corporate re-organization(3)	(4.58)	
Pro forma net tangible book value per share as of June 30, 2018 before new investors purchasing ADSs in this offering	2.33	
Effect attributable to new investors purchasing ADSs in this offering(4)	1.82	
Pro forma as adjusted net tangible book value per ADS as of June 30, 2018		4.15
Dilution per share to new investors purchasing ADSs in this offering		$10.85

(1) 154,369 outstanding ordinary shares were included in this calculation to give effect to the issuance of ordinary shares subsequent to June 30, 2018.
(2) 13,924,474 outstanding ordinary shares were included in this calculation to give effect to the sale of our Series C convertible preferred shares for net cash proceeds of $148.0 million in August 2018 and subsequent conversion of these shares into ordinary shares.
(3) 69,761,485 outstanding ordinary shares were included in the dilution per share calculation attributable to the corporate reorganization, (including the Series C convertible preferred shares).
(4) 83,094,818 outstanding ordinary shares were included in the dilution per share calculation attributable to new investors purchasing ADSs in this offering.

Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, would increase (decrease) our pro forma as adjusted net tangible book value as of June 30, 2018 after this offering by $0.15 per ADS, and would increase (decrease) dilution to new investors by $0.85 per ADS, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. An increase (decrease) of 1,000,000 in the number of ADSs we are offering would increase (decrease) our pro forma as adjusted net tangible book value as of September 30,

2018 after this offering by $0.12 per ADS, and would increase (decrease) dilution to new investors by $0.12 per ADS, assuming the assumed initial public offering price per ADS remains the same. The pro forma as adjusted information is illustrative only, and we will adjust this information based on the actual initial public offering price and other terms of this offering determined at pricing.

If the underwriters exercise their option to purchase additional ADSs in full, the pro forma as adjusted net tangible book value per ADS after the offering would be $4.38, the increase in net tangible book value per ADS to existing shareholders would be $4.38 and the immediate dilution in net tangible book value per ADS to new investors in this offering would be $10.62.

The following table summarizes, on the pro forma as adjusted basis described above as of June 30, 2018, the differences between the existing shareholders and the new investors in this offering with respect to the number of ordinary shares purchased from us (including ordinary shares underlying ADSs), the total consideration paid to us and the average price per ordinary share (including ordinary shares underlying ADSs), based on an assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, before deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

	Ordinary shares/ ADSs purchased		Total consideration		Average price per ordinary shares/ADS
	Number	Percent	Amount	Percent	
Existing shareholders	69,761,485	84.0%	$285,603,621	58.8%	$ 4.09
New investors participating in this offering	13,333,333	16.0%	200,000,000	41.2%	$ 15.00
Total	83,094,818	100.0%	$485,603,621	100.0%	

Each $1.00 increase (decrease) in the assumed initial public offering price of $15.00 per ADS, which is the midpoint of the price range on the cover page of this prospectus, would increase or decrease the total consideration paid by new investors by $13.3 million and, in the case of an increase, would increase the percentage of total consideration paid by new investors by 1.6 percentage points and, in the case of a decrease, would decrease the percentage of total consideration paid by new investors by 1.7 percentage points, assuming that the number of ADSs offered by us, as set forth on the cover page of this prospectus, remains the same. An increase (decrease) of 1,000,000 in the number of ADSs offered by us, as set forth on the cover page of this prospectus, would increase or decrease the total consideration paid by new investors by $15.0 million and, in the case of an increase, would increase the percentage of total consideration paid by new investors by 1.7 percentage points and, in the case of a decrease, would decrease the percentage of total consideration paid by new investors by 1.9 percentage points, assuming no change in the assumed initial public offering price per ADS.

If the underwriters exercise their option to purchase additional ADSs in full, the percentage of ordinary shares held by existing shareholders will decrease to 55.4% of the total number of ordinary shares outstanding after the offering, and the number of shares held by new investors will be increased to 15,333,332, or 18.0% of the total number of ordinary shares outstanding after this offering.

The table and discussion above exclude additional ordinary shares reserved for future issuance under our 2018 Plan, which will become effective upon the signing of the underwriting agreement related to this offering, as well as any automatic increases in the number of ordinary shares reserved for issuance under the 2018 Plan and any contingent issuances under existing agreements providing for the issuance of shares based on achievement of performance milestones.

To the extent that options are issued under our 2018 Plan, or we issue additional ordinary shares or ADSs in the future, there will be further dilution to investors participating in this offering.

Selected consolidated financial data

The following tables present the selected consolidated financial data as of the dates and for the periods indicated for Orchard Therapeutics Limited. We derived the selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2016 and 2017 and the consolidated balance sheet data as of December 31, 2016 and 2017 from our audited consolidated financial statements included elsewhere in this prospectus and, other than pro forma and supplemental pro forma amounts, do not reflect the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The consolidated statements of operations data for the six months ended June 30, 2017 and 2018 and the consolidated balance sheet data as of June 30, 2018 have been derived from our unaudited condensed consolidated financial statements included elsewhere in this prospectus and have been prepared on the same basis as the audited consolidated financial statements and, other than pro forma and supplemental pro forma amounts, do not reflect the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. In the opinion of management, the unaudited data reflects all adjustments, consisting only of normal recurring adjustments, necessary for a fair statement of the financial information contained in those statements. We prepare our consolidated financial statements in accordance with U.S. GAAP. Our historical unaudited condensed consolidated financial statements as of and for the six months ended June 30, 2018 have been restated. See Note 1 to the unaudited condensed consolidated financial statements included elsewhere in this prospectus.

Our historical results are not necessarily indicative of our future results. You should read this data together with our consolidated financial statements and related notes appearing elsewhere in this prospectus and the information under the sections titled “Capitalization” and “Management’s discussion and analysis of financial condition and results of operations.”

Our functional currency is the pound sterling. However, for financial reporting purposes, our financial statements, which are prepared using the functional currency, have been translated into U.S. dollars. Our assets and liabilities are translated at the exchange rates at the balance sheet date, our revenue and expenses are translated at average exchange rates and shareholders’ equity is translated based on historical exchange rates. Translation adjustments are not included in determining net loss but are included in foreign exchange translation adjustment within accumulated other comprehensive (loss) income, a component of shareholders’ equity.

Foreign currency transactions in currencies different from the functional currency are translated into the functional currency using the exchange rates prevailing at the dates of the transactions. Foreign exchange differences resulting from the settlement of such transactions and from the translation at period-end exchange rates of monetary assets and liabilities denominated in foreign currencies are recorded in other expense in the statement of operations and comprehensive loss.

As of June 29, 2018, the last business day of the period ended June 30, 2018, the representative exchange rate was £1.00 = $1.3197.

In August 2018, Orchard Rx Limited was incorporated under the laws of England and Wales to become the holding company for Orchard Therapeutics Limited pursuant to our corporate reorganization. See “Corporate reorganization.” Prior to this offering, Orchard Rx Limited has only engaged in activities incidental to its formation, the corporate reorganization and this offering. Prior to the completion of this offering, we intend to re-register Orchard Rx Limited as a public limited company and change our name from Orchard Rx Limited to Orchard Therapeutics

plc. Following the corporate reorganization, the historical consolidated financial statements of Orchard Therapeutics plc will be retrospectively adjusted to include the historical financial results of Orchard Therapeutics Limited for all periods presented.

	Year ended December 31,		Six months ended June 30,	
	2016	2017	2017	2018 (as restated)
	(in thousands, except share and per share data)			
Consolidated Statement of Operations and Comprehensive Loss Data:				
Operating expenses:				
Research and development	$ 16,206	$ 32,527	$ 10,546	$ 160,162
General and administrative	2,997	5,985	2,270	11,948
Total operating expenses	19,203	38,512	12,816	172,110
Loss from operations	(19,203)	(38,512)	(12,816)	(172,110)
Other income (expense), net	138	(1,179)	(400)	401
Net loss before income taxes	(19,065)	(39,691)	(13,216)	(171,709)
Income tax expense	(20)	(53)	42	165
Net loss attributable to ordinary shareholders	$ (19,085)	$ (39,744)	$ (13,174)	$ (171,544)
Other comprehensive (loss) income:				
Foreign currency translation adjustment	(271)	4,398	2,070	1,970
Total comprehensive loss	$ (19,356)	$ (35,346)	$ (11,104)	$ (169,574)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.15)	$ (3.58)	$ (1.24)	$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	8,872,333	11,086,808	10,648,967	12,615,109
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)(1)	$ (2.69)	$ (4.48)	$ (1.55)	$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)(1)	7,100,528	8,872,768	8,522,366	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shares, basic and diluted (unaudited)(2)		$ (1.24)		$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)(2)		32,056,206		49,349,711

	As of December 31,		As of June 30, 2018
	2016	2017	(as restated)
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash	$ 3,497	$ 89,856	$ 48,762
Working capital(3)	163	83,466	15,770
Total assets	4,283	97,294	64,646
Convertible preferred shares in temporary equity	16,970	—	—
Total shareholders' (deficit) equity	(16,524)	86,405	14,746

(1) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the years ended December 31, 2016 and 2017, and for the six months ended June 30, 2017 and 2018, give effect to the 1-for-0.8003 reverse split of all ordinary shares as part of the corporate reorganization. Such pro forma data will become the historical net loss per share attributable to ordinary shares, basic and diluted, of Orchard Therapeutics plc upon consummation of the corporate reorganization.

(2) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the periods ended December 31, 2017 and June 30, 2018 give effect to (i) the automatic conversion of all outstanding convertible preferred shares, as if the conversion had occurred at the later of January 1, 2017 or the issuance dates of the preferred shares, and (ii) the 1-for-0.8003 reverse split of all ordinary and convertible preferred shares; further, the shares to be sold in the proposed offering are excluded from the unaudited pro forma basic and diluted loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the year ended December 31, 2017 and the period ended June 30, 2018. See Note 10 to our audited financial statements included in this prospectus for further details on the calculation of unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders.

(3) We define working capital as current assets less current liabilities.

Management's discussion and analysis of financial condition and results of operations

You should read the following discussion and analysis of our financial condition and results of operations together with the "Selected consolidated financial data" section and our financial statements and the related notes included at the end of this prospectus. Our historical unaudited condensed consolidated financial statements as of and for the six months ended June 30, 2018 have been restated. See Note 1 to the unaudited condensed consolidated financial statements included elsewhere in this prospectus. Some of information contained in this discussion and analysis or set forth elsewhere in this prospectus, including statements of our plans, objectives, expectations and intentions, contain forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk factors" section of this prospectus, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. Please also see the section titled "Special note regarding forward-looking statements."

In August 2018, Orchard Rx Limited was incorporated under the laws of England and Wales to become the holding company for Orchard Therapeutics Limited pursuant to our corporate reorganization. See "Corporate reorganization." Prior to this offering, Orchard Rx Limited has only engaged in activities incidental to its formation, the corporate reorganization and this offering. Accordingly, a discussion and analysis of the results of operations and financial condition of Orchard Rx Limited for the period of its operations prior to the corporate reorganization would not be meaningful and are not presented. Prior to the completion of this offering, we intend to re-register Orchard Rx Limited as a public limited company and to change our name from Orchard Rx Limited to Orchard Therapeutics plc. Following the corporate reorganization, the historical consolidated financial statements of Orchard Therapeutics plc will be retrospectively adjusted to include the historical financial results of Orchard Therapeutics Limited for all periods presented.

Overview

We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous hematopoietic stem cells, or HSCs, into a gene-modified drug product to treat the patient's disease through a single administration. We achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process, resulting in a drug product that can then be re-introduced into the patient at the bedside.

To date, our commercial product and clinical-stage product candidates have been administered in over 150 patients across five different diseases. These results, in combination with our deep expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially transformative therapies to patients suffering from a broad range of rare diseases.

We are initially focusing our autologous *ex vivo* gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Our portfolio currently includes Strimvelis, our commercial-stage gammaretroviral-based product for the treatment of ADA-SCID, five lentiviral product candidates

in clinical-stage development and several other product candidates in preclinical development. We expect to submit a BLA with the FDA for our product candidate OTL-101, a lentiviral gene therapy for ADA-SCID, in 2020, followed by an MAA with the EMA. We also plan to submit an MAA with the EMA for our next most advanced clinical candidate, OTL-200 for the treatment of MLD, in 2020 followed by a BLA with the FDA.

Beyond these three lead product candidates, our other clinical-stage programs OTL-102 for X-CGD and OTL-300 for TDBT have been generally well-tolerated and have demonstrated clinical activity in initial clinical trials. We are also expanding our neurometabolic disorders franchise with the development of two preclinical programs, OTL-201 for MPS-IIIA, and OTL-202 for MPS-IIIB. We anticipate filing a CTA with the applicable regulatory agency in Europe for MPS-IIIA by the end of 2019 and to continue to progress preclinical development of MPS-IIIB.

Since our inception in 2015, we have devoted substantially all of our resources to conducting research and development of our product candidates, in-licensing and acquiring rights to our product candidates, business planning, raising capital and providing general and administrative support for our operations. To date, we have financed our operations primarily with proceeds from the sale of convertible preferred shares. Through June 30, 2018, we had received gross proceeds of $137.6 million from sales of our convertible preferred shares.

We have incurred significant operating losses since our inception in 2015. With the exception of our commercial product Strimvelis, which was acquired in April 2018, we will not generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for our product candidates. Our net losses were $19.1 million, $39.7 million and $171.5 million for the years ended December 31, 2016 and 2017 and the six months ended June 30, 2018, respectively. As of June 30, 2018, we had an accumulated deficit of $230.9 million. These losses have resulted primarily from costs incurred in connection with research and development activities and general and administrative costs associated with our operations. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future.

As a result, we will need substantial additional funding to support our continuing operations and pursue our growth strategy. Until such time as we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of equity offerings, debt financings, collaborations, government contracts or other strategic transactions. We may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If we fail to raise capital or enter into such agreements as, and when, needed, we may have to significantly delay, scale back, or discontinue the development and commercialization of one or more of our programs.

Recent developments

Our agreement with GSK

In April 2018, we entered into the GSK Agreement, with GSK, pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS, and OTL-300, a clinical-stage gene therapy program for TDBT, and in connection with which we acquired non-exclusive rights to certain third-party intellectual property, including rights related to lentiviral vector technology to develop and commercialize OTL-200 for MLD and OTL-103 for

WAS. In addition, GSK novated to us their R&D Agreement with Telethon-OSR, which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Milan, Italy for MPS-I, CGD and GLD.

Under the GSK Agreement, we are required to use our best endeavors to continue to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in the European Union, and at all times at the San Raffaele Hospital in Milan, Italy provided that a minimum number of patients continue to be treated at this site. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement. In addition, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we are required to first use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and submit an MAA or BLA, as applicable, for OTL-300 for TDBT in either the United States or Europe.

We paid GSK a one-time upfront fee of £10.0 million under the GSK Agreement, issued to GSK 15,563,230 Series B-2 convertible preferred shares (before the 1-for-0.8003 reverse split to be effected prior to completion of this offering) and have a payable due to GSK of £4.9 million under this agreement.

In connection with our transaction with GSK in April 2018, we recorded a liability for Strimvelis representing the fair value of the future expected costs to maintain the marketing authorization in excess of the expected future sales. See Note 8 to our unaudited condensed consolidated financial statements appearing at the end of this prospectus for additional details of the GSK Agreement and the accounting for this agreement.

Our agreement with Telethon-OSR

In connection with our agreement with GSK, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement for the research, development and commercialization of *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDBT, X-CGD, MPS-I and GLD.

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicenseable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, worldwide license to develop and commercialize vectors and gene therapy products for the treatment of WAS, MLD, TDBT, X-CGD, MPS-I and GLD. At the time we entered into the deed and novation agreement, GSK had completed development, launched and commercialized Strimvelis for ADA-SCID in Europe, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to the WAS, MLD and TDBT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the WAS, MLD and TDBT collaboration programs pursuant to the GSK Agreement and the deed of novation.

Issuance of Series C convertible preferred shares

In August 2018, we received net cash proceeds of $148.0 million from the sale of our Series C convertible preferred shares. See "—Liquidity and capital resources."

Components of our results of operations

Revenue

Since inception through June 30, 2018, we had not generated revenue from product sales for sales of Strimvelis. We do not expect to generate any revenue from the sale of products, with the exception of Strimvelis, in the near future. If our development efforts for our product candidates that we may develop in the future are successful and result in regulatory approval, or collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from collaboration or license agreements.

Operating expenses

Research and development expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts and the development of our product candidates, and include:

- expenses incurred under agreements with third parties, including CROs that conduct research, preclinical activities and clinical trials on our behalf as well as CMOs that manufacture lentiviral vectors and cell-based drug products for use in our preclinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing preclinical study and clinical trial materials;
- costs related to compliance with regulatory requirements;
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs; and
- upfront, milestone and management fees for maintaining licenses under our third-party licensing agreements.

In January 2017, we and UCLA, executed a subcontract agreement, whereby we provide UCLA certain research and development services related to autologous lentiviral gene therapy in ADA-SCID as part of UCLA's existing ADA-SCID research program that is being funded by CIRM. The total reimbursement we may receive under this agreement is $10.4 million, which may be received during the period from January 2017 to December 2021. The reimbursement is recognized as a reduction in research and development expense for research activities that have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. In the event we have performed reimbursable research activities and have not been reimbursed, it is recognized within prepaid expenses and other current assets.

We expense research and development cost as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of

the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as a prepaid expense or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. See "—Income tax (expense) benefit."

In 2016 and 2017, we issued ordinary shares to various academic and health care institutions as part of the consideration for entering into several license agreements to in-license intellectual property rights and know-how relevant to our programs. This consideration was accounted for as research and development expense based on the fair value of the shares issued as of the time the agreements were executed.

Our direct external research and development expenses are tracked on a program-by-program basis and consist of costs, such as fees paid to consultants, contractors and CMOs in connection with our preclinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred prior to designating a product candidate are included in other program expense. We do not allocate employee costs, costs associated with our discovery efforts, laboratory supplies, and facilities, including depreciation or other indirect costs, to specific product development programs because these costs are deployed across multiple product development programs and, as such, are not separately classified.

Research and development activities are central to our business model. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will continue to increase for the foreseeable future as a result of our expanded portfolio of product candidates and as we: (i) expedite the clinical development and obtain marketing approval for our lead product candidates, including OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS; (ii) initiate additional clinical trials for our product candidates, including OTL-102 for X-CGD and OTL-300 for TDBT; (iii) improve the efficiency and scalability of our manufacturing processes and supply chain; and (iv) build our in-house process development, analytical and manufacturing capabilities and continue to discover and develop additional product candidates. We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

As a result of the GSK Agreement, in the six-month period ended June 30, 2018, we recognized a charge to research and development expense of $133.6 million related to the acquisition of in-process research and development programs that have no future alternative use. See Note 7 to our unaudited condensed consolidated financial statements appearing at the end of this prospectus for additional details of the GSK Agreement and its accounting.

The successful development of our product candidates and commercialization of our commercial product and product candidates, if approved, is highly uncertain. This is due to the numerous risks and uncertainties associated with product development and commercialization, including the following:

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;

- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Strimvelis and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and compliance systems;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, EMA or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant trial delays due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development and we may never succeed in obtaining regulatory approval for any of our product candidates.

General and administrative expenses

General and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, corporate and business development and administrative functions. General and administrative expenses also include professional fees for legal, patent, accounting, auditing, tax and consulting services, travel expenses and facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities and other operating costs.

We expect that our general and administrative expenses will increase in the future as we increase our general and administrative headcount to support our continued research and development and potential commercialization of our expanded portfolio of product candidates. We also expect to incur increased expenses associated with being a public company, including costs of accounting, audit, legal, regulatory and tax compliance services, director and officer insurance costs and investor and public relations costs.

Other income (expense), net

Interest income

Interest income consists of income earned on our cash. Our interest income has not been significant.

Change in fair value of tranche obligations

In 2016, Series A convertible preferred shares were issued in three tranches, and tranche obligations were recognized for the obligations related to the second and third tranches, which were measured at fair value at each reporting date. We recognized changes in fair value of these tranche obligations as a component of other income (expense) in our consolidated statement of operations and comprehensive loss. The tranche obligation liabilities were satisfied when the respective second and third tranche of Series A convertible preferred shares closed in July 2016 and January 2017.

Other income (expense)

Other income (expense), net consists primarily of realized and unrealized foreign currency transaction gains and losses.

Income tax (expense) benefit

We are subject to corporate taxation in the United States and the United Kingdom. Due to the nature of our business, we have generated losses since inception and have therefore not paid United Kingdom corporation tax. Our income tax (expense) benefit represents only income taxes in the United States.

The research and development tax credit received in the United Kingdom is recorded as a credit against R&D expenses. The UK research and development tax credit, as described below, is fully refundable to Company and is not dependent on current or future taxable income. As a result, we have recorded the entire benefit from the UK research and development tax credit as a reduction to R&D expenses and is not reflected as part of the income tax provision. If, in the future, any UK research and development tax credits generated are needed to offset a corporate income tax liability in the UK, that portion would be recorded as a benefit within the income tax provision and any refundable portion not dependent on taxable income would continue to be recorded as a reduction to research and development expenses.

As a company that carries out extensive research and development activities, we seek to benefit from one of two U.K. research and development tax credit cash rebate regimes: the SME Program and the RDEC Program. Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which we do not receive income.

Based on criteria established by HM Revenue and Customs, or HMRC, we expect a portion of expenditures being carried in relation to our pipeline research and development, clinical trials management and manufacturing development activities to be eligible for the RDEC Program for the years ended December 31, 2016 and 2017 and six months ended June 30, 2018. The Company will assess whether it is possible to qualify under the more favorable SME regime for future accounting periods, but this may be affected as a result of becoming a United States public company.

Unsurrendered U.K. losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of U.K. taxable profits. After accounting for tax credits receivable, we had accumulated tax losses for carry forward in the United Kingdom of $48.4 million as of December 31, 2017.

In the event we generate revenues in the future, we may benefit from the U.K. “patent box” regime that allows profits attributable to revenues from patents or patented products to be taxed at effective rate of 10%.

Value Added Tax, or VAT, is broadly charged on all taxable supplies of goods and services by VAT-registered businesses. Under current rates, an amount of 20% of the value, as determined for VAT purposes, of the goods or services supplied is added to all sales invoices and is payable to HMRC. Similarly, VAT paid on purchase invoices is generally reclaimable from HMRC.

Results of operations

Comparison of the years ended December 31, 2016 and 2017

The following table summarizes our results of operations for the years ended December 31, 2016 and 2017:

	Year ended December 31,		
	2016	2017	Change
	(in thousands)		
Operating expenses:			
Research and development	$ 16,206	$ 32,527	$ 16,321
General and administrative	2,997	5,985	2,988
Total operating expenses	19,203	38,512	19,309
Loss from operations	(19,203)	(38,512)	(19,309)
Other (expense) income:			
Interest income	3	—	(3)
Change in fair value of tranche obligations	289	—	(289)
Other (expense) income, net	(154)	(1,179)	(1,025)
Total other (expense) income	138	(1,179)	(1,317)
Net loss before income tax	(19,065)	(39,691)	(20,626)
Income tax expense	(20)	(53)	(33)
Net loss attributable to ordinary shareholders	$(19,085)	$(39,744)	$(20,659)

Research and development expenses

The table below summarizes our research and development expenses by product candidate or development program:

	Year ended December 31,		
	2016	2017	Change
	(in thousands)		
Direct research and development expenses by program:			
OTL-101 for ADA-SCID	$ 7,468	$13,181	$ 5,713
OTL-102 for X-CGD	—	1,303	1,303
OTL-201 for MPS-IIIA	3,565	3,158	(407)
Other programs	1,548	4,938	3,390
Research and discovery and unallocated costs			
Personnel related (including share-based compensation)	1,892	6,770	4,878
Facility and other	1,733	3,177	1,444
Total research and development expenses	$16,206	$32,527	$16,321

Direct research and development expenses relating to OTL-101 increased by $5.7 million in 2017, primarily driven by increased manufacturing costs of $9.4 million to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials and increased clinical costs of $3.5 million to prepare and activate clinical trial sites. The increase was offset by $4.3 million of reimbursements received in 2017 as part of our subcontract agreement with UCLA and a $2.9 million decrease in in-licensing fees in 2017 as a majority of the OTL-101 related in-licensing transactions took place in 2016.

Direct costs related to OTL-102 in 2017 consist of the costs of in-licensing the technology relevant to the program, which included our commitment to issue 437,049 ordinary shares to the licensor.
Direct research and development expenses relating to OTL-201 decreased by $0.4 million in 2017. The decrease primarily relates to a decrease in in-licensing fees of $3.0 million in 2017 as all in-licensing transactions relevant to this program took place in 2016. This decrease is offset by an increase in OTL-201 manufacturing costs of $2.4 million and clinical costs of $0.2 million, as a result of increasing clinical research activities.

Direct research and development expenses for other programs increased by $3.4 million in 2017, primarily related to an increase in manufacturing costs of $3.7 million as we prepare certain programs for clinical trials. The increase was offset by a $0.2 million decrease in preclinical costs and a $0.1 million decrease in in-licensing fees.

The increase of $6.3 million in unallocated research and development expenses was attributable to personnel-related costs, including share-based compensation, which was primarily due to an increase in headcount in our research and development functions. Personnel-related costs for each of the year ended December 31, 2016 and 2017 included share-based compensation expense of $0.2 million and $0.6 million, respectively. In 2017, the personnel related costs have been reduced by $0.7 million of reimbursements received as part of our subcontract agreement with UCLA. Facility and other costs increased primarily due to the lease of new laboratory space and the increased costs of supporting the increased headcount in our research and development functions and their research efforts.

General and administrative expenses

General and administrative expenses were $3.0 million for the year ended December 31, 2016, compared to $6.0 million for the year ended December 31, 2017. The increase of $3.0 million was primarily due to increased personnel-related costs of $2.1 million from an increased headcount in our general and administrative function. Share-based compensation expense of less than $0.1 million and $0.4 million is included in general and administrative expense for the year ended December 31, 2016 and 2017, respectively. Professional and consulting fees increased by $0.5 million in 2017 as a result of an increase in accounting, audit and information technology fees as well as costs associated with ongoing business activities. Facility and other costs increased $0.4 million in 2017, primarily due to the lease of new office space and increased costs of supporting the expansion of our business.

Other income (expense), net

Other income (expense), net for the years ended December 31, 2016 and 2017 was income of $0.1 million and expense of $1.2 million, respectively. During the year ended December 31, 2017, as our business activities increased in the United States and Europe, realized and unrealized foreign currency loss increased by $1.0 million. The year ended December 31, 2016 also included $0.3 million of other income in 2016 from the change in fair value of tranche obligations, which was associated with our obligation to issue the second and third tranches of Series A convertible preferred shares. We settled the final tranche obligation in early 2017 and there was no change in fair value recorded in the year ended December 31, 2017.

Comparison of the six months ended June 30, 2017 and 2018

The following table summarizes our results of operations for the six months ended June 30, 2017 and 2018:

	Six months ended June 30,		
	2017	2018 (as restated)	Change
	(in thousands)		
Operating expenses:			
Research and development	$ 10,546	$ 160,162	$ 149,616
General and administrative	2,270	11,948	9,678
Total operating expenses	12,816	172,110	159,294
Loss from operations	(12,816)	(172,110)	(159,294)
Other income (expense):			
Other income (expense), net	(400)	401	801
Total other income (expense)	(400)	401	801
Net loss before income tax	(13,216)	(171,709)	(158,493)
Income tax expense	42	165	123
Net loss attributable to ordinary shareholders	$(13,174)	$ (171,544)	$(158,370)

Research and development expenses

The table below summarizes our research and development expenses by product candidate or development program:

	Six months ended June 30,		
	2017	2018 (as restated)	Change
	(in thousands)		
Direct research and development expenses by program:			
OTL-200 for MLD.	$ —	$ 72,009	$ 72,009
OTL-103 for WAS.	—	66,339	66,339
OTL-101 for ADA-SCID	4,646	9,487	4,841
OTL-102 for X-CGD	—	940	940
OTL-201 for MPS-IIIA	1,392	480	(912)
Other programs	318	3,031	2,713
Research and discovery and unallocated costs			
Personnel related (including share-based compensation)	2,797	4,936	2,139
Facility and other	1,393	2,940	1,547
Total research and development expenses	$10,546	$ 160,162	$149,616

In April 2018, GSK transferred OTL-200, OTL-103 and OTL-102 to us resulting in increased direct research and development expenses of $72.0 million, relating to OTL-200, and $66.3 million, relating to OTL-103, and $0.9 million, relating to OTL-102 in the six months ended June 30, 2018.

The increase of $72.0 million, relating to OTL-200, consists of a $69.3 million of in-process research and development charges related to the GSK transaction along with $1.2 million of clinical trial costs and $0.8 million of costs to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials.

The increase of $66.3 million, relating to OTL-103, consists of a $64.3 million of in-process research and development charges related to the GSK transaction along with $1.0 million of clinical trial costs and $1.3 million of costs to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials.

Direct research and development expenses relating to OTL-101 increased by $4.8 million in the six months ended June 30, 2018, primarily due to increased manufacturing costs of $2.0 million to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials, increased clinical costs of $1.9 million to prepare and activate clinical trial sites, a decrease of $0.8 million in reimbursements received in 2018 as part of our subcontract agreement with UCLA and a $0.1 million increase in licensing fees in 2018.

Increased direct research and development expenses relating to OTL-102 in the six months ended June 30, 2018 are primarily due to manufacturing costs of $0.6 million to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials and clinical trial costs of $0.3 million to prepare and activate clinical trial sites.

Direct research and development expenses relating to OTL-201 decreased by $0.9 million in the six months ended June 30, 2018. The decrease primarily relates to a decrease of $0.7 million in manufacturing and process development costs associated with our viral vector and cell manufacturing processes and a decrease of $0.2 million in preclinical development expenses.

Direct research and development expenses for other programs increased by $2.7 million in the six months ended June 30, 2018. $2.3 million of the increase relates to ongoing clinical trial and manufacturing costs for Strimvelis, which was transferred from GSK to us in April 2018 pursuant to our agreement with GSK. $0.4 million of the increase relates to clinical trial costs for OTL-300, transferred from GSK, to prepare and activate clinical trial sites.

The increase of $3.7 million in unallocated research and development expenses was attributable to personnel-related costs, including share-based compensation, which was primarily due to an increase in headcount in our research and development functions. Personnel-related costs for each of the six months ended June 30, 2017 and 2018 included share-based compensation expense of $0.2 million and $0.7 million, respectively. In 2018, the personnel related costs have been reduced by $1.1 million of reimbursements received as part of our subcontract agreement with UCLA. Facility and other costs increased primarily due to the lease of new laboratory space and the increased costs of supporting the increased headcount in our research and development functions and their research efforts.

General and administrative expenses

General and administrative expenses were $2.3 million for the six months ended June 30, 2017, compared to $12.0 million for the six months ended June 30, 2018. The increase of $9.7 million was primarily due to increased personnel related costs of $3.9 million for additional options granted after June 30, 2017 and an increased headcount in our general and administrative function. Share-based compensation expense of less than $0.1 million and $1.6 million is included in general and administrative expense for the six months ended June 30, 2017 and 2018, respectively. Professional and consulting fees increased by $2.9 million during the six months ended June 30, 2018 as a result of an increase in accounting, audit and information technology fees as well as costs associated with ongoing business activities. Facility and other costs increased $3.0 million during the six months ended June 30, 2018, primarily due to the lease of new office space and increased costs of supporting the expansion of our business.

Other income (expense), net

Other income (expense), net for the six months ended June 30, 2017 and 2018 was $(0.4) million and income of $0.4 million, respectively. During the six months ended June 30, 2017, as our business activities increased in the United States and United Kingdom, we incurred realized and unrealized foreign currency loss of approximately $0.4 million. During the six months ended June 30, 2018, the U.S. Dollar depreciated versus the pounds sterling, resulting in a foreign currency gain of approximately $0.4 million.

Liquidity and capital resources

From our inception through June 30, 2018, we did not generate any revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We currently have only one commercial product, Strimvelis, which we acquired from GSK in April 2018 and our product candidates are in various phases of preclinical and clinical development. We do not expect to generate significant revenue from sales of any products for several years, if at all. To date, we have financed our operations primarily with proceeds from the sale of convertible preferred shares and reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from CIRM.

Through June 30, 2018, we had received gross proceeds of $137.6 million from sales of convertible preferred shares and reimbursement of $7.3 million from our subcontract agreement with UCLA. As of June 30, 2018, we had cash of $48.8 million. In August 2018, we received net cash proceeds of $148.0 million from the sale of our Series C convertible preferred shares.

We currently have no ongoing material financing commitments, such as lines of credit or guarantees, that are expected to affect our liquidity over the next five years, other than our manufacturing and lease obligations described below.

Cash flows

The following table summarizes our cash flows for each of the periods presented:

	Year ended December 31,		Six months ended June 30,	
	2016	2017	2017	2018 (as restated)
	(in thousands)			
Net cash used in operating activities	$(14,566)	$ (32,487)	$(14,634)	$ (41,075)
Net cash used in investing activities	(190)	(1,559)	(663)	(2,833)
Net cash provided by financing activities	18,034	115,696	44,609	2,275
Effect of exchange rate changes on cash	(751)	4,709	2,102	539
Net increase in cash	$ 2,527	$ 86,359	$ 31,414	$ (41,094)

Operating activities

During the six months ended June 30, 2017, operating activities used $14.6 million of cash, primarily resulting from our net loss of $13.2 million, increased by net cash used by changes in our operating assets and liabilities of $1.9 million, and offset by net non-cash charges of $0.5 million, which included $0.3 million of share-based compensation expenses. Net cash used by changes in our operating assets and liabilities for the six months ended June 30, 2017 is primarily due to the impact of a $7.2 million increase in other receivables related to the UCLA funding agreement and $1.0 million increase in prepaid expenses and other current assets, offset by a $1.3 million increase in accounts payable and a $5.0 million increase in accrued expenses and other current liabilities.

During the six months ended June 30, 2018, operating activities used $41.1 million of cash, primarily resulting from our net loss of $171.5 million, off-set by net cash provided by changes in our operating assets and liabilities of $34.3 million and net non-cash charges of $96.1 million, which included $93.4 million for the issuance of our preferred shares as non-cash in-license fees under the GSK Agreement. Net cash provided by changes in our operating assets and liabilities for the six months ended June 30, 2018 is primarily due to the impact of a $9.9 million increase in accounts payable and a $22.8 million increase in accrued expenses and other current liabilities, offset by a $7.8 million decrease in other long-term liabilities, and a $6.0 million increase in prepaid and other assets. Included within operating activities was payment of $14.2 million for the GSK upfront license fee.

During the year ended December 31, 2016, operating activities used $14.6 million of cash, primarily resulting from our net loss of $19.1 million, offset by net cash provided by changes in our operating assets and liabilities of $1.5 million and net non-cash charges of $3.0 million, which included $3.1 million for the issuance of our ordinary shares as non-cash in-license fees. Net cash

provided by changes in our operating assets and liabilities for the year ended December 31, 2016 is primarily due to the impact of a $0.6 million increase in prepaid expenses and other current assets, offset by a $0.7 million increase in accounts payable and a $1.5 million increase in accrued expenses and other current liabilities. Net cash used in operating activities for the year ended December 31, 2016 included $4.6 million of cash payments for in-licensing technology fees.

During the year ended December 31, 2017, operating activities used $32.5 million of cash, primarily resulting from our net loss of $39.7 million, net cash provided by changes in our operating assets and liabilities of $2.8 million and net non-cash charges of $4.4 million, which included $3.1 million for the issuance of our ordinary shares as non-cash in-license fees and $1.0 million of share-based compensation. Net changes in our operating assets and liabilities for the year ended December 31, 2017 consisted primarily of a $1.2 million increase in other receivables and a $2.7 million increase in prepaid expenses and other current assets, offset by a $1.9 million increase in accounts payable and a $4.7 million increase in accrued expenses. Net cash used in operating activities for the year ended December 31, 2017 included $1.2 million of cash payments for in-licensing technology fees.

The change in net cash used in operating activities from 2016 to 2017 is the result of our increased net loss, generally due to growth in our business and the advancement of our development programs, as described in "—Results of operations."

Investing activities

During the six months ended June 30, 2017 and 2018, we used $0.7 million and $2.8 million, respectively, of cash in investing activities for purchases of property and equipment.

During the years ended December 31, 2016 and 2017, we used $0.2 million and $1.6 million, respectively, of cash in investing activities for purchases of property and equipment.

Financing activities

During the six months ended June 30, 2017, net cash provided by financing activities was $44.6 million, consisting of $8.6 million of net proceeds from the sale of our Series A convertible preferred shares in January 2017 and $36.0 million of net proceeds from the sale of our Series B convertible preferred shares issued during the six months ended June 30, 2017.

During the six months ended June 30, 2018, net cash provided by financing activities was $2.3 million, primarily consisting of $2.2 million of net proceeds from the sale of our Series B convertible preferred shares during the six months ended June 30, 2018.

During the year ended December 31, 2016, net cash provided by financing activities was $18.0 million, consisting of net proceeds from the sale of our Series A convertible preferred shares.

During the year ended December 31, 2017, net cash provided by financing activities was $115.7 million, consisting of $8.6 million of net proceeds from the sale of our Series A convertible preferred shares in January 2017 and $107.1 million of net proceeds from the sale of our Series B convertible preferred shares issued throughout 2017.

Funding requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates and as we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of Strimvelis in the European Union, and any product candidates for which we may submit for and obtain marketing approval anywhere in the world;
- continue our development of our product candidates, including continuing our ongoing advanced registrational trials and supporting studies of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and our ongoing clinical trials of OTL-102 for X-CGD and OTL-300 for TDBT, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- conduct IND and CTA-enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates and to support manufacturing of product to commercial scale;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel; and
- develop, maintain, expand and protect our intellectual property portfolio; and transition our organization to being a public company.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve or maintain profitability. Even if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe that the anticipated net proceeds from this offering, together with our existing cash, will enable us to fund our operating expenses and capital expenditure requirements into the second half of 2020. We have based this estimate on assumptions that may prove to be wrong, and we could exhaust our available capital resources sooner than we expect.

Because of the numerous risks and uncertainties associated with the development of product candidates and programs, and because the extent to which we may enter into collaborations

with third parties for development of our product candidates is unknown, we are unable to estimate the timing and amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our future capital requirements will depend on many factors, including:

- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities required, including quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution, to support Strimvelis in the European Union and any other products for which we obtain marketing approval;
- qualifying for, and maintaining adequate coverage and reimbursement by, government and payors on a timely basis for Strimvelis and any other products for which we obtain marketing approval;
- the costs of preparing and submitting marketing approvals for any of our product candidates that successfully complete clinical trials, and the costs of maintaining marketing authorization and related regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, preclinical development and clinical trials for our product candidates;
- our ability to enroll clinical trials in a timely manner and to quickly resolve any delays or clinical holds that may be imposed on our development programs;
- the costs associated with our manufacturing process development and evaluation of third-party;
- manufacturers and suppliers;
- the costs, timing and outcome of regulatory review of our product candidates;
- revenue, if any, received from commercial sales of Strimvelis and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims; and
- the terms of our current and any future license agreements and collaborations; and the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, government contracts or other strategic transactions. To the extent that we raise additional capital through the sale of equity, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as an ordinary shareholder. Preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends. If we raise additional funds through collaboration agreements, strategic alliances, licensing arrangements or marketing and distribution arrangements, we may have to relinquish valuable

rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market products or product candidates that we would otherwise prefer to develop and market ourselves.

Contractual obligations and commitments

The following table summarizes our contractual obligations as of December 31, 2017 and the effects that such obligations are expected to have on our liquidity and cash flows in future periods:

	Payments due by period				
	Total	Less than 1 year	1 to 3 years	4 to 5 years	More than 5 years
			(in thousands)		
Manufacturing commitments(1)	$3,240	$ 2,160	$1,080	$ —	$ —
Operating lease commitments(2)	$3,633	$ 1,359	$2,274	$ —	$ —
Total	$6,873	$ 3,519	$3,354	$ —	$ —

(1) Amounts reflect commitments for costs associated with our external CMO, which we engaged to manufacture clinical trial materials. Our manufacturing commitment included non-cancelable minimum quantities to be purchased as of December 31, 2017.

(2) Amounts reflect minimum payments due for our office and laboratory space leases. We have one office lease in London, U.K. and one office lease in Manchester, U.K. under operating leases that expire between January 2019 and January 2023. We lease laboratory space in Foster City, California, Menlo Park, California, and Los Angeles, California under operating leases that expire between June 2018 and October 2021.

We enter into contracts in the normal course of business with CMOs and other third parties for clinical trials and preclinical research studies and testing. Manufacturing commitments in the preceding table include agreements that are enforceable and legally binding on us and that specify all significant terms, including fixed or minimum quantities to be purchased, fixed, minimum or variable price provisions, and the approximate timing of the transaction. For obligations with cancellation provisions, the amounts included in the preceding table are limited to the non-cancelable portion of the agreement terms or the minimum cancellation fee.

Excluding our agreement with GSK, we may incur potential contingent payments totaling up to $68.0 million upon our achievement of clinical, regulatory and commercial milestones, as applicable, or royalty payments that we may be required to make under license agreements we have entered into with various entities pursuant to which we have in-licensed certain intellectual property. Pursuant to our agreement with Oxford BioMedica, we may incur the obligation to issue additional ordinary shares upon the achievement of a certain development milestone. Due to the uncertainty of the achievement and timing of the events requiring payment under these agreements, the amounts to be paid by us are not fixed or determinable at this time and are excluded from the table above.

In January 2018, we leased additional office space in London, United Kingdom, with a term through January 2023. The annual rental commitment is approximately $0.8 million. In March 2018, we leased office space in Boston, Massachusetts, with a term through September 2022. The annual rental commitment is approximately $0.3 million.

Under the GSK Agreement, we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired by GSK and OTL-101. We will pay a mid-single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digit to the low teens for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048.

As consideration for the licenses and options in the Telethon-OSR agreements acquired and assumed in the Transaction, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are also required to pay Telethon-OSR a fee in connection with the exercise of our option for each collaboration program. We are obligated to pay up to an aggregate of €31.0 million in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDBT programs) and we may become obligated to pay up to an aggregate of €70.5 million in connection with option fees and product development milestones with respect to those programs for which we have not to date exercised our exclusive license option under this agreement (that is, for X-CGD, MPS-I and GLD programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs.

Critical accounting policies and significant judgments and estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with U.S. GAAP. The preparation of our consolidated financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in greater detail in Note 2 to our consolidated financial statements appearing at the end of this prospectus, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Fair value of asset acquisitions

We assign fair value to the tangible and intangible assets acquired and liabilities assumed based upon their estimated fair values as of the acquisition date. The purchase price allocation process requires management to make significant estimates and assumptions, especially at the acquisition date with respect to intangible assets and in-process research and development ("IPR&D").

Accrued research and development expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel to identify services that have been performed on our behalf and estimating the level of service performed and the associated cost incurred for the service when we have not yet been invoiced or otherwise notified of actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advanced payments. We make estimates of our accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- Vendors in connection with performing research activities on our behalf and conducting preclinical studies and clinical trials on our behalf;
- CMOs in connection with the production of preclinical and clinical trial materials;
- investigative sites or other service providers in connection with clinical trials;
- vendors in connection with preclinical and clinical development activities; and
- vendors related to product manufacturing and development and distribution of preclinical and clinical supplies.

We base our expenses related to preclinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CMOs, research institutions and vendors that supply, conduct and manage preclinical studies and clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses.

Fair value measurements—tranche obligations

As part of the Series A subscription and shareholder agreement in 2016, we committed to issue additional Series A convertible preferred shares in two tranches at £1.00, upon the achievement of specified milestones. We concluded that the tranche obligations were freestanding financial instruments that were required to be separately recorded at the date the Series A subscription and shareholder agreement was executed. The tranche obligations were accounted for as liabilities at their fair values and then to be remeasured at each balance sheet date, with changes in fair value to be recorded in other income (expense). As a result, the tranche obligations were recorded as a liability in the amount of $2.5 million in February 2016. The tranche obligations were partially settled in July 2016, at which time the liability-classified portion of the tranche obligations was remeasured at its fair value and reclassified to additional paid-in capital. The remaining tranche obligations were settled in January 2017. Aggregate changes in fair value recognized in 2016 resulted in non-cash other income of $0.3 million.

The fair values of the tranche obligations were based on significant inputs not observable in the market. We used the Black-Scholes option-pricing model, which incorporates assumptions and estimates, to value the tranche obligations. We assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions is obtained. Estimates and assumptions impacting the fair value measurement include the fair value per share of the underlying convertible preferred shares, the remaining contractual term of each tranche obligations, risk-free interest rate, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares. We determine the fair value per share of the underlying convertible preferred shares by taking into consideration our most recent sales of our convertible preferred shares, results obtained from third-party valuations and additional factors that we deem relevant. We are a private company that lacks company-specific historical and implied volatility information for our shares. Therefore, we estimate expected share volatility based on the historical volatility of publicly traded peer companies for a term equal to the expected term of the applicable tranche obligation. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve for time periods approximately equal to the expected term of the applicable tranche obligation. We have estimated a 0% dividend yield based on the expected dividend yield and the fact that we have never paid or declared dividends. Significant changes to the fair value of the underlying share would have resulted in a significant change in the fair value measurements.

Share-based compensation

We measure share-based awards granted to employees, non-employees and directors based on the fair value on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, we issue share-based awards with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have not issued any share-based awards with performance-based vesting conditions.

Prior to the adoption of Accounting Standards Update (ASU) No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (ASU 2018-07), as discussed in Note 2 to our consolidated financial statements appearing at the end of this prospectus, the measurement date for non-employee awards was generally the date the services are completed, resulting in financial reporting period adjustments to stock-based

compensation during the vesting terms for changes in the fair value of the awards. After adoption of ASU 2018-07, the measurement date for non-employee awards is the later of the adoption date of ASU 2018-07, or the date of grant, without change in the fair value of the award.

Determination of the fair value of ordinary shares

As there has been no public market for our ordinary shares to date, the estimated fair value of our ordinary shares has been determined by our board of directors as of the date of each option grant, with input from management, considering third-party valuations of our ordinary shares as well as our board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant.

The fair value of each share option is estimated on the date of grant using the Black-Scholes option pricing model. We historically have been a private company and lack company-specific historical and implied volatility information for our shares. Therefore, we estimate our expected share price volatility based on the historical volatility of publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our own traded share price. The expected term of our share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options. Prior to the adoption of ASU 2018-07, the expected term of share options granted to non-employees was the contractual term. After adoption of ASU 2018-07, the expected term of share options granted to non-employees is determined in the same manner as share options granted to employees. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that we have never paid cash dividends on our ordinary shares and do not expect to pay any cash dividends in the foreseeable future.

The third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. Our ordinary share valuations were prepared using either an option pricing method, or OPM, or a hybrid method, both of which used market approaches to estimate our enterprise value. The OPM treats ordinary shares and convertible preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the ordinary shares have value only if the funds available for distribution to shareholders exceeded the value of the preferred share liquidation preferences at the time of the liquidity event, such as a strategic sale or a merger. A discount for lack of marketability of the ordinary shares is then applied to arrive at an indication of value for the ordinary share. The hybrid method is a probability-weighted expected return method, PWERM, where the equity value in one or more scenarios is calculated using an OPM. The PWERM is a scenario-based methodology that estimates the fair value of ordinary shares based upon an analysis of future values for the company, assuming various outcomes. The ordinary share value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each class of share. The future value of the ordinary shares under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the ordinary share. These third-party valuations

were performed at various dates, which resulted in valuations of our ordinary shares (in each instance, not reflecting the 1-for-0.8003 reverse share split that will be part of our corporate reorganization) of $0.38 per share as of July 31, 2016, $0.75 per share as of September 30, 2016, $1.95 per share as of February 28, 2017, $2.36 per share as of May 31, 2017, $2.97 per share as of October 31, 2017, $3.79 per share as of April 11, 2018, $5.21 per share as of June 21, 2018, $5.68 per share as of July 21, 2018 and August 1, 2018, $7.25 as of August 31, 2018 and September 13, 2018, and $8.24 as of September 25, 2018. Our board of directors considered various objective and subjective factors to determine the fair value of our ordinary shares as of each grant date, including:

- the prices at which we sold preferred share and the superior rights and preferences of the convertible preferred shares relative to our ordinary shares at the time of each grant;
- the progress of our research and development programs, including the status of preclinical studies and planned clinical trials for our product candidates;
- our stage of development and our business strategy;
- external market conditions affecting the biotechnology industry, and trends within the biotechnology industry;
- our financial position, including cash on hand, and our historical and forecasted performance and operating results;
- the lack of an active public market for our ordinary and convertible preferred shares;
- the likelihood of achieving a liquidity event, such as an initial public offering, or IPO, or a sale of our company in light of prevailing market conditions; and
- the analysis of IPOs and the market performance of similar companies in the biopharmaceutical industry.

The assumptions underlying these valuations represent management's best estimates, which involve inherent uncertainties and the application of management judgment. As a result, if factors or expected outcomes change and we use significantly different assumptions or estimates, our share-based compensation expense could be materially different.

Once a public trading market for our ordinary shares has been established in connection with the closing of this offering, it will no longer be necessary for our board of directors to estimate the fair value of our ordinary shares in connection with our accounting for granted share options and other such awards we may grant, as the fair value of our ordinary shares will be determined based on the quoted market price of our ordinary shares.

Options granted

The following table sets forth, by grant date, the number of shares subject to options granted from January 1, 2017 through October 4, 2018, the per share exercise price of the options, the fair value of ordinary shares per share on each grant date, and the per share estimated fair value of the options: The information set forth below does not reflect the 1-for-0.8003 reverse share split that will be part of our corporate reorganization.

Grant date	Number of shares subject to options granted	Per share exercise price of options(1)	Fair value per ordinary share on grant date	Per share estimated fair value of options(2)
April 28, 2017(3)	334,350	$ 1.95	$ 1.95	$ 1.41
April 28, 2017(3)	193,750	£ 0.00001	$ 1.95	$ 1.95
July 1, 2017(3)	110,000	$ 1.95	$ 2.36	$ 1.75
July 1, 2017(3)	372,000	£ 0.00001	$ 2.36	$ 2.36
September 1, 2017(3)	50,000	$ 1.95	$ 2.36	$ 1.82
September 1, 2017(3)	11,000	£ 0.00001	$ 2.36	$ 2.36
October 26, 2017(3)	1,967,635	$ 1.95	$ 2.97	$ 2.30
February 7, 2018(3)	1,565,788	$ 1.95	$ 3.79	$ 2.84
February 7, 2018(3)	1,116,743	£ 0.00001	$ 3.79	$ 3.79
March 26, 2018(3)	465,750	$ 1.95	$ 3.79	$ 2.83
March 26, 2018(3)	94,750	£ 0.00001	$ 3.79	$ 3.79
June 12, 2018(4)	882,250	$ 3.79	$ 5.21	$ 3.62
June 12, 2018(4)	262,000	£ 0.00001	$ 5.21	$ 5.21
July 21, 2018	68,100	£ 0.00001	$ 5.68	$ 5.68
July 21, 2018	393,500	$ 5.68	$ 5.68	$ 3.53
August 1, 2018	10,700	£ 0.00001	$ 5.68	$ 5.68
August 1, 2018	98,000	$ 5.68	$ 5.68	$ 3.54
August 31, 2018	48,000	£ 0.00001	$ 7.25	$ 7.25
August 31, 2018	470,500	$ 7.25	$ 7.25	$ 4.40
September 13, 2018	738,692	£ 0.00001	$ 7.25	$ 7.25
September 13, 2018	1,257,896	$ 7.25	$ 7.25	$ 4.45
September 25, 2018	136,000	£ 0.00001	$ 8.24	$ 8.24
September 25, 2018	106,500	$ 8.24	$ 8.24	$ 5.07

(1) The Per Share Exercise Price of options granted to our U.S. employees represents the per share fair value of our ordinary shares on the date of grant, as determined by our board of directors, after considering our most recently available contemporaneous valuation of our ordinary shares as well as additional factors that may have changed since the date of such contemporaneous valuation through the date of grant. The Per Share Exercise Price of options granted to U.K. employees equal to the nominal value of our ordinary shares of £0.00001.

(2) The Per Share Estimated Fair Value of Options reflects the weighted-average fair value of options granted on each grant date, determined using the Black-Scholes option-pricing model.

(3) At the time of the option grants on April 28, 2017, July 1, 2017, September 1, 2017, October 26, 2017, February 7, 2018 and March 26, 2018, our board of directors determined that the fair value of our ordinary shares of $1.95 per share, calculated in the contemporaneous valuation as of February 28, 2017, reasonably reflected the per share fair value of our ordinary shares as of the grant dates. The fair value of the ordinary shares at the date of these grants was adjusted to $2.36, $2.97 and $3.79 per share, as presented, in connection with a retrospective fair value assessment for financial reporting purposes.

(4) At the time of the option grants on June 12, 2018, our board of directors determined that the fair value of our ordinary shares of $3.79 per share, calculated in the contemporaneous valuation as of April 11, 2018, reasonably reflected the per share fair value of our ordinary shares as of the grant dates. The fair value of the ordinary shares at the date of these grants was adjusted to $5.21 per share, as presented, in connection with a retrospective fair value assessment for financial reporting purposes.

Grants of stock options under the 2016 Plan

From July 1, 2018 to September 14, 2018, we granted options to employees and one of our new directors for the purchase of an aggregate of 3,085,388 ordinary shares, at a weighted average exercise price of $4.97 per share, not reflecting the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The aggregate grant-date fair value of these options was $15.6 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

On September 25, 2018, we granted options to employees and consultants for the purchase of an aggregate of 242,500 ordinary shares, at a weighted average exercise price of $3.62 per share, not reflecting the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The aggregate grant-date fair value of these options was $1.7 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

Income taxes

We account for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in our tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. We assess the likelihood that our deferred tax assets will be recovered in the future and, to the extent we believe, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies. See Note 9 to our consolidated financial statements appearing at the end of this prospectus for additional information.

We are subject to corporate taxation in the United Kingdom and the United States. The calculation of our tax provision involves the application of both U.K. or U.S. tax law and requires judgement and estimates.

We account for uncertainty in income taxes in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed as the amount of benefit to recognize in the consolidated financial statements. The amount of benefits that may be used is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes included the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate, as well as the related net interest and penalties.

We record United Kingdom research and development tax credits as a reduction to research and development expense in the year in which the expenditures were incurred. The research and development tax credits are not dependent on us generating future taxable income, our ongoing tax status, or tax position. We have recorded an offset to research and development expense of

$0.2 million and $0.7 million for the years ended December 31, 2016 and 2017, respectively. We have recorded an offset to research and development expense of $0.2 million and $3.6 million for the six months ended June 30, 2017 and 2018, respectively.

The refund is denominated in pounds sterling and, therefore, the receivable is remeasured into U.S. dollars as of each reporting date. As of December 31, 2016, and 2017 and June 30, 2018, our tax incentive receivable from the U.K. government was $0.1 million, $0.9 million and $4.1 million, respectively. These amounts have not yet been received from the HMRC.

Quantitative and qualitative disclosures about market risks

Interest rate sensitivity

As of June 30, 2018, we had cash of $48.8 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying U.K. and U.S. bank interest rates. Our surplus cash has been invested in interest-bearing savings accounts from time to time. We have not entered into investments for trading or speculative purposes. Due to the conservative nature of our investment portfolio, which is predicated on capital preservation of investments with short-term maturities, we do not believe an immediate one percentage point change in interest rates would have a material effect on the fair market value of our portfolio, and therefore we do not expect our operating results or cash flows to be significantly affected by changes in market interest rates.

As of June 30, 2018, we had no debt outstanding and are therefore not subject to interest rate risk related to debt.

Foreign currency exchange risk

We maintain our consolidated financial statements in our functional currency, which is the pounds sterling. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency at rates of exchange prevailing at the balance sheet dates. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income (loss) for the respective periods. We recorded foreign currency losses of $0.2 million and $1.2 million for the years ended December 31, 2016 and 2017, respectively, and foreign currency losses of $0.4 million and foreign currency gains of $0.4 million for the six months ended June 30, 2017 and 2018, respectively. These foreign currency transaction gains and losses are included in other expense in our consolidated statements of operations and comprehensive loss.

For financial reporting purposes, our consolidated financial statements have been translated into U.S. dollars. Assets and liabilities have been translated at the exchange rates at the balance sheet dates, while revenue and expenses are translated at the average exchange rates over the reporting period and shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net income (loss) but are included in our foreign exchange adjustment to other comprehensive loss, a component of shareholders' equity.

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future. Instruments that may be used to hedge future risks include foreign currency forward and swap contracts. These instruments may be used to selectively manage risks, but there can be no assurance that we will be fully protected against material foreign currency fluctuations.

Emerging growth company status

We are an “emerging growth company,” as defined in the JOBS Act, and we may take advantage of reduced reporting requirements that are otherwise applicable to public companies. We may take advantage of these exemptions until we are no longer an emerging growth company. Section 107 of the JOBS Act provides that an emerging growth company can take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards. We have elected to use the extended transition period for complying with new or revised accounting standards; and as a result of this election, our financial statements may not be comparable to companies that comply with public company effective dates. We may take advantage of these exemptions up until the last day of the fiscal year following the fifth anniversary of this offering or such earlier time that we are no longer an emerging growth company. We would cease to be an emerging growth company if we have more than $1.07 billion in annual revenue, we have more than $700.0 million in market value of our share held by non-affiliates (and we have been a public company for at least 12 months and have filed one annual report on either Form 10-K or Form 20-F), or we issue more than $1.0 billion of non-convertible debt securities over a three-year period. In relation to the extended transition period, we will continue to adopt new or revised standards at the time private companies adopt the new standard and will do so until such time that we either (i) irrevocably “opt out” of such extended transition period or (ii) no longer qualify as an emerging growth company. While we have not made such an irrevocable election, we have not delayed the adoption of any applicable accounting standards.

In addition, we intend to rely on the other exemptions and reduced reporting requirements provided by the JOBS Act. Subject to certain conditions set forth in the JOBS Act, we are entitled to rely on certain exemptions as an “emerging growth company,” we are not required to, among other things, (i) provide an auditor’s attestation report on our system of internal controls over financial reporting pursuant to Section 404(b), (ii) provide all of the compensation disclosure that may be required of non-emerging growth public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) comply with any requirement that has or may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements (auditor discussion and analysis), and (iv) disclose certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the chief executive officer’s compensation to median employee compensation. These exemptions will apply for a period of five years following the completion of this offering or until we no longer meet the requirements of being an emerging growth company, whichever is earlier.

Off-balance sheet arrangements

We did not have during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC.

Recently issued accounting pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our consolidated financial statements appearing at the end of this prospectus.

Business

Overview

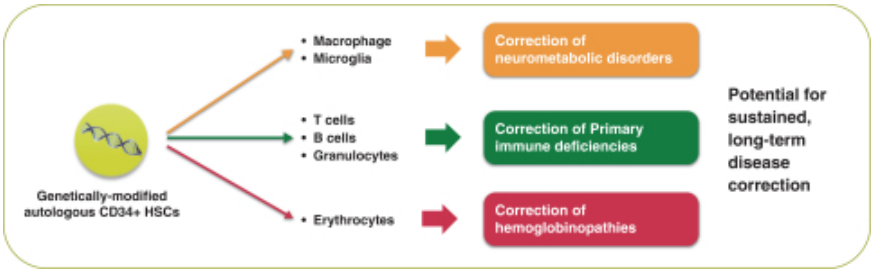
We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, HSCs into a gene-modified drug product to treat the patient's disease through a single administration. We achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process, resulting in a drug product that can then be re-introduced into the patient at the bedside.

To date, our commercial product and clinical-stage product candidates have been administered in over 150 patients across five different diseases. These results, in combination with our deep expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially transformative therapies to patients suffering from a broad range of rare diseases.

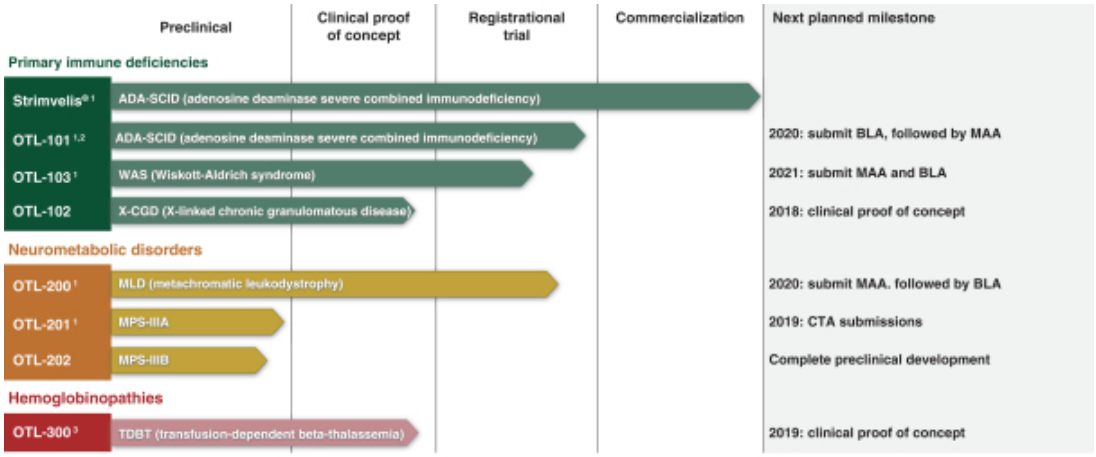
We are initially focusing our autologous *ex vivo* gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Our portfolio currently includes Strimvelis, our commercial-stage gammaretroviral-based product for the treatment of ADA-SCID five lentiviral product candidates in clinical-stage development and several other product candidates in preclinical development. We anticipate making near-term regulatory submissions for approval of three of our most advanced clinical-stage product candidates. These include OTL-101 for the treatment of ADA-SCID, OTL-200 for the treatment of MLD and OTL-103 for the treatment of WAS.

We intend to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. The indications we are initially targeting in our primary immune deficiencies and neurometabolic franchises (ADA-SCID, MLD, WAS, X-CGD, and MPS-IIIA) alone have a combined annual incidence rate of between 1,000 and 2,000 patients in markets around the world where treatments for rare diseases are often reimbursed. Based on this, we believe the total addressable market potential in the diseases areas underlying our five lead programs could be greater than $2 billion annually. In addition, certain indications such as X-CGD and WAS have large existing populations with pre-existing disease that could be eligible for our treatments upon receiving marketing approval, which could increase the size of our market opportunity further.

We believe our approach of using lentiviral vectors to genetically modify HSCs has wide-ranging applicability to a large number of indications. The ability of HSCs to differentiate into multiple cell types allows us to deliver gene-modified cells to multiple physiological systems, including the central nervous system, immune system and red blood cell lineage, thereby potentially enabling the correction of a wide range of diseases. By leveraging the innate self-renewing capability of HSCs as well as the ability of lentiviral vectors to achieve stable integration of a modified gene into the chromosomes of HSCs, our gene therapies have the potential to provide a durable effect following a single administration.



We have a broad and advanced portfolio of wholly-owned commercial and development stage products and product candidates. In April 2018, we strengthened our portfolio with our acquisition of Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT from Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD, or, together, GSK.



1: Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher (U.S.)
2: Breakthrough Therapy Designation
3: Priority Medicines (PRIME) Designation

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare or ultra-rare indications, we believe our clinical programs will generally be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. For purposes of this prospectus, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial.

We currently anticipate making submissions for regulatory approval of each of our three lead product candidates within the next three years. For each of these lead product candidates, we are in ongoing discussions with the applicable regulatory authorities with respect to the clinical and other data required for regulatory submission.

As of September 2018, over 150 patients have been treated across our commercial and clinical-stage programs. The table below reflects the total number of patients treated the maximum follow-up and the range of patient follow-up as of September 2018 across the lead programs in our franchise areas.

Franchise	Program	Patients treated with gene therapy[1]	Follow-up post gene therapy (minimum)	Follow-up post gene therapy (maximum)[2]
Primary immune deficiencies	**OTL-101** (ADA-SCID)	61	0.2 years	6.5 years
	Strimvelis® (ADA-SCID)	24	0.2 years	18.0 years
	OTL-103 (WAS)	16	0.0 years	8.2 years
	OTL-102 (X-CGD)	10	1.1 years	2.8 years
Neurometabolic disorders	**OTL-200** (MLD)	31	0.0 years	8.3 years
Hemoglobinopathies	**OTL-300** (TDBT)	9	0.8 years	3.0 years
Total		151		

(1) The number of patients reflects all patients treated in the development phase, including in clinical trials and compassionate use. We refer to patients treated through a compassionate use, early access or hospital exemption or special license program as compassionate use patients.

(2) Published literature in our franchise areas indicate that, left untreated, each of our lead target indications carries significant risk of mortality: (i) ADA-SCID patients have a mortality rate of 14% at one year of age and 33% at two years of age; (ii) late infantile MLD patients and juvenile MLD patients have mortality rates of 50% and 44%, at five years of age and 10 years of age, respectively, (iii) WAS patients have a mortality rate of 62% at 15 years of age, (iv) X-CGD patients have a mortality rate of 40% at 35 years of age, and (v) left untreated, mortality in TDBT patients generally occurs within the first three years of life. We believe follow-up data across our five clinical-stage programs support the transformative nature of our approach in indications that are almost always fatal in early life without treatment.

The diseases we are targeting affect patients around the world, requiring an infrastructure to deliver gene therapies globally. We are therefore building a commercial-scale manufacturing infrastructure and leveraging technologies that will allow us to deliver our gene therapies globally in a fully-integrated manner. In order to meet anticipated demand for our growing pipeline of product candidates and planned product offerings, we are initially utilizing our existing network of CMOs to manufacture vectors and drug product. In addition, we currently operate two development laboratory facilities in California and plan to invest in additional facilities to accommodate our expanding technical operations and implement in-house drug product and vector manufacturing capabilities.

Cryopreservation of our gene-modified HSCs is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide, facilitating both local treatment and local product reimbursement. In anticipation of commercialization, we have developed cryopreserved formulations of our three most advanced product candidates and are working to demonstrate comparability to the fresh cell formulations used in our registrational trials. We are also establishing cryopreserved product formulations for all of our earlier stage product candidates.

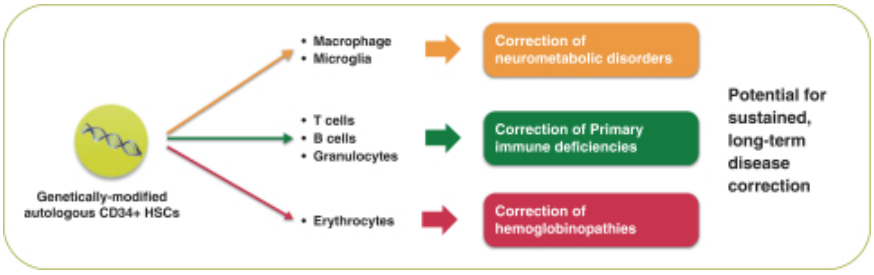
We have global commercial rights to Strimvelis and all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe, subject to obtaining necessary marketing approvals in those jurisdictions. We plan to deploy a focused commercial infrastructure to deliver our product candidates to patients, and are focused on working closely with all relevant stakeholders, including patients, caregivers, specialist physicians and payors, to ensure the widest possible post-approval access for our product candidates.

As we continue to develop and expand our portfolio, we believe that the deep experience of our management team and our extensive academic relationships are key strategic strengths. Our management team has over 100 years of collective experience in rare diseases and in the manufacturing, preclinical and clinical development and commercialization of gene and cell therapies. In addition, we partner with leading academic institutions, which are pioneers in autologous *ex vivo* gene therapy. We plan to leverage our internal expertise combined with our relationships with leading academic institutions to transition our lead clinical-stage product candidates to commercialization and continue to expand our portfolio of autologous *ex vivo* gene therapy products for rare diseases.

Our autologous *ex vivo* gene therapy approach

Our *ex vivo* gene therapy approach seeks to transform a patient's autologous HSCs into a gene-modified drug product to treat the patient's disease. HSCs are self-renewing cells that are capable of differentiating into all types of blood cells, including white blood cells, red blood cells and platelets. HSCs can be obtained directly from the bone marrow, which requires administration of a general anesthetic, or from the patient's peripheral blood with the use of a mobilizing agent that can move HSCs from the bone marrow into the peripheral blood. By delivering gene-modified HSCs back to patients, we seek to take advantage of the self-renewing capability of HSCs to enable a durable effect following a single administration, as has been seen in our development programs. In addition, the ability of HSCs to differentiate into multiple different cell types has the potential to enable the delivery of gene-modified cells to different physiological systems and allow the correction of a range of different diseases.

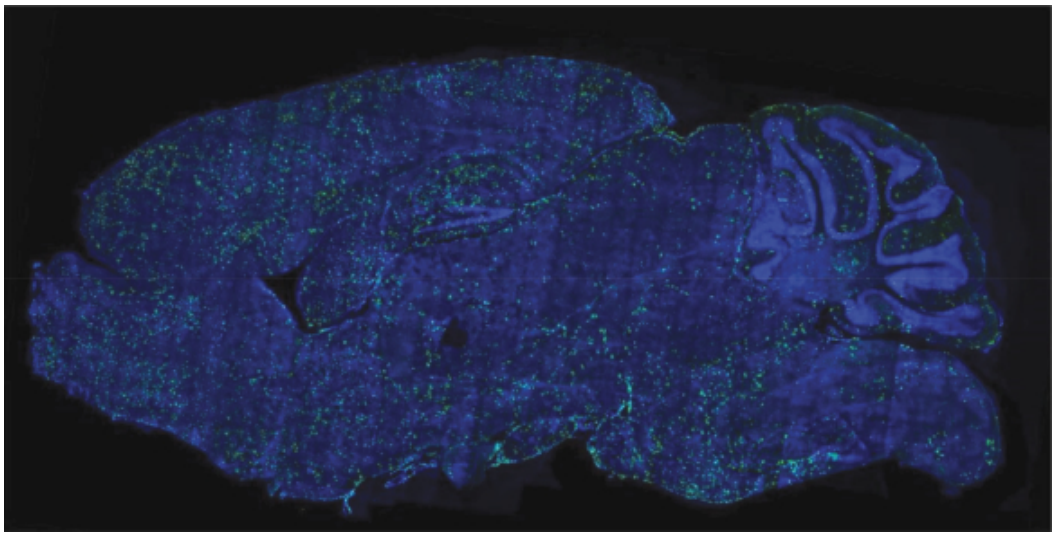
Clinical validation already exists for HSCT, an approach of treating a patient with HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations, including difficulties in finding appropriate genetically-matched donors and the risk of transplant-related rejection and mortality, and is therefore typically only offered on a limited basis. Our approach is intended to address the significant limitations of HSCT.



One example of the potential of our autologous *ex vivo* gene therapy approach to deliver genes to different physiological systems is demonstrated below. In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America,* or *PNAS*, a subpopulation of gene-modified HSCs have evidenced the potential to cross the blood-brain barrier, engraft in the brain as microglia and express genes and proteins within the central nervous system. As published in *PNAS*, the image below shows a cross-section of the brain of a mouse that received green fluorescent protein, or GFP, gene-modified HSCs intravenously. The GFP expression observed throughout the brain denotes the potential of gene-modified HSCs to cross the blood-brain barrier and express the functional protein

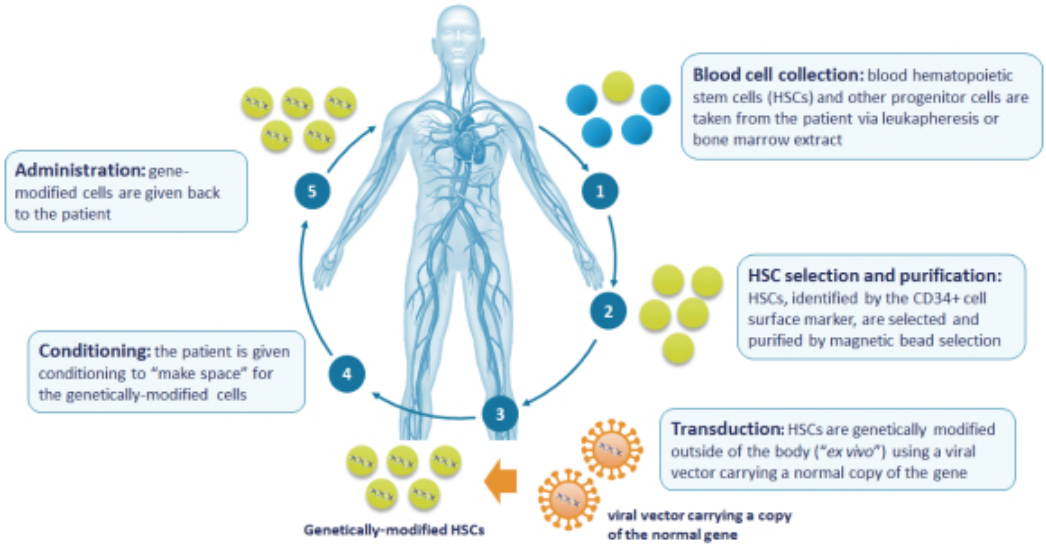
throughout the brain, thereby potentially addressing a range of indications that affect the central nervous system. Our OTL-200 program for MLD leverages this same mechanism of action to deliver gene-modified HSCs through the blood-brain barrier and deliver a therapeutic gene that can prevent neuronal degeneration.

Transgene distribution in brain of mouse model following administration of HSCs transduced with GFP encoding vector



With respect to each of our product candidates, our *ex vivo* gene therapy approach utilizes a non-replicating lentiviral vector to introduce a functional copy of the missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process called transduction, resulting in drug product that can then be re-introduced into the patient. Unlike other viral vectors, such as adeno-associated viral, or AAV, vectors, lentiviral vectors integrate into the chromosomes of patients' HSCs. We believe this allows us to achieve stable integration of the modified gene into the HSCs and to achieve durable expression of the target protein by the gene-modified HSCs after a single administration of gene therapy. Strimvelis, our commercial-stage product, utilizes an older generation gammaretroviral vector.

The image below illustrates the steps in our approach to transform a patient's autologous HSCs *ex vivo* into therapeutic product.



Initial clinical trials conducted using our product candidates utilized a fresh product formulation, resulting in a limited drug product shelf life. We plan to market our current and future product candidates, if approved, in a cryopreserved product formulation to enable the shipment of the drug product to specialized treatment centers throughout the world, allowing patients to receive treatment closer to their home. The cryopreservation also allows us to conduct a number of quality control tests on the modified HSCs prior to introducing them into the patient.

In addition, certain of our clinical-stage product candidates have been evaluated in registrational trials using drug product derived from HSCs extracted from the patients' bone marrow. To optimize our potential product label and commercial presence, as part of any BLA or MAA submission for such product candidates, we plan to demonstrate comparability between drug product manufactured using HSCs derived from the patients' peripheral blood and drug product manufactured using HSCs derived from the patients' bone marrow in these cases where clinical trials were conducted using vector and/or drug product manufactured at academic centers, we plan to demonstrate comparability between vector and/or drug product manufactured by our selected third party CMOs with vector and drug product manufactured at such academic centers.

Initially, we are employing our autologous *ex vivo* gene therapy approach to three target franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Data from clinical trials suggests that autologous *ex vivo* gene therapy has the potential to provide well-tolerated and sustainable results over existing standards of care for diseases in these target franchise areas. We believe that we can apply our approach beyond our initial target indications to treat a broad range of rare diseases.

Our strengths

We believe that the combination of our growing body of clinical data evidencing the potential of our autologous *ex vivo* gene therapy approach, and our deep expertise in the development,

manufacturing and commercialization of gene and cell therapies, positions us well to provide potentially transformative therapies through a single administration to patients suffering from a broad range of rare diseases. We believe our key strengths include:

- **Durable, sustained therapeutic potential:** Durable and sustained clinical activity has been observed in patients in each of our lead programs across five different diseases following a single administration. For example, our commercial-stage gammaretroviral program, Strimvelis, has demonstrated sustained recovery of the immune system, resulting in survival over approximately 18 years after a single administration. As of July 2018, overall survival has been observed in a maximum follow-up of approximately six years in patients treated with our lentiviral gene therapy OTL-101 for ADA-SCID and approximately eight years in patients treated with our lentiviral gene therapies OTL-200 for MLD and OTL-103 for WAS. Without treatment, these indications are almost always fatal early in life.

- **Demonstrated safety record:** Our autologous *ex vivo* gene therapy approach, has been well-tolerated in patients treated to date. Lentiviral vectors have a history of safety in clinical trials, with no reported instances of insertional mutagenesis or leukemogenesis in patients for more than 10 years. Our *ex vivo* modification of the patient's own HSCs also allows us to engineer and test the patient's cells prior to administering the therapy to the patient. Over 150 patients have been treated with our commercial product and clinical-stage product candidates, and each of these therapies has been well-tolerated overall, with no suspected unexpected serious adverse reactions, or SUSARs, related to the drug products observed to date. Of these over 150 patients, 127 patients were treated with our lentiviral-based clinical-stage programs. The most common adverse reactions observed in clinical trials across these programs have included pyrexia and infections. We believe that the long-term extensive follow-up across multiple different diseases and with vectors expressing different genes demonstrates the potential safety of our autologous *ex vivo* gene therapy approach.

  Our autologous *ex vivo* gene therapy approach offers important advantages over HSCT, which is the standard of care for several of the indications that we are targeting. HSCT carries a significant risk of complications and mortality. In order to make bone marrow space for incoming donor cells, patients undergoing HSCT need to receive conditioning often involving two to three chemotherapy agents that are associated with significant short- and long-term organ toxicities. In our autologous *ex vivo* gene therapy approach, we employ a milder conditioning regimen, which is associated with reduced toxicity and length of hospitalization. HSCT also requires the identification of a well-matched third-party donor to provide the cells. A poor cell donor match can result in graft rejection or acute and chronic graft-versus-host disease, or GvHD, a serious complication of HSCT in which the third party donor's immune cells identify the cells of the patient as "foreign" and attack them. GvHD is a severe autoimmune reaction that can lead to organ failure and death. In general, a higher degree of mismatch between the donor and the recipient is associated with a greater risk of disease or graft rejection; however, a well-matched cell transplant can still result in GvHD. By using the patient's own cells, our autologous *ex vivo* gene therapies eliminate the risk of GvHD or graft rejection by providing the patient with a perfect cell match.

- **Applicability to a potentially large number of patients and indications:** A core part of our mission is to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. We believe our autologous *ex vivo* gene therapy approach has broad therapeutic potential across a large number of rare diseases in our target franchise areas. The lentiviral vectors that we employ in our clinical-stage programs have large capacity

payloads that have the potential to introduce a target gene of choice into the patient's HSCs. The transduction of these vectors into a patient's own HSCs allows for the potentially life-long production of gene-modified HSCs in the body and thus distribution of the target gene throughout multiple organs and tissues, including across the central nervous system.

- **Our deep expertise in gene therapy and rare diseases:** Our management team has over 100 years of collective experience in rare diseases and the manufacturing, preclinical and clinical development and commercialization of gene and cell therapies. Members of our executive leadership team have held senior positions at GSK, Shire, BioMarin, Alexion, Sangamo Therapeutics, PTC Therapeutics, StemCells Inc., Osiris, PCT Cell Therapy Services and other companies specializing in gene and cell therapies and rare diseases. In addition, we partner with academic institutions that are pioneers in autologous *ex vivo* gene therapy and we have obtained exclusive licenses to extensive preclinical data, clinical data and know-how to build our portfolio of autologous *ex vivo* gene therapies. These partnerships with leading institutions such as UCLA, Boston Children's Hospital and the NIH in the United States, and UCL, GOSH, Telethon Institute of Gene Therapy, San Raffaele Hospital, The University of Manchester, the Manchester Foundation Trust, and Généthon in Europe, are a core part of our research engine through which we are advancing our lead clinical-stage programs and working to identify opportunities with comparably high probabilities of success. We plan to leverage our internal expertise combined with our relationships with leading academic institutions to transition our lead clinical-stage product candidates from the academic setting to commercial-ready production and further expand our pipeline.

Our strategy

Our mission is to transform the lives of patients with rare genetic diseases using our autologous *ex vivo* gene therapy approach. We are building a leading, global, fully-integrated gene therapy company focused on serious and life-threatening rare diseases. To achieve this, we are pursuing the following strategies:

- **Advance our five clinical-stage product candidates towards marketing approvals:** Our pipeline currently includes five clinical-stage programs including three in advanced registrational trials. We plan to submit a BLA with the FDA for our product candidate OTL-101 for ADA-SCID in 2020, followed by an MAA with the EMA. Our programs OTL-200 for MLD and OTL-103 for WAS have both achieved their primary endpoints in registrational trials. Though the primary endpoints in these registrational trials have been achieved, patient follow-up remains ongoing in accordance with the trial protocols. We plan to submit an MAA for our product candidate OTL-200 with the EMA in 2020, followed by a BLA with the FDA, and we intend to submit an MAA with the EMA and a BLA with the FDA for our product candidate OTL-103 in 2021. Furthermore, our clinical-stage programs OTL-102 for X-CGD and OTL-300 for TDBT continue to be generally well-tolerated and generate clinical activity data in initial clinical trials, and, assuming these trials are successful, we plan to advance these programs through clinical development to regulatory submission.
- **Leverage the power of our therapeutic approach to expand our product pipeline across multiple indications:** Through our clinical trials, we believe we have exhibited the potential of our autologous *ex vivo* gene therapy approach to target multiple physiological systems in the human body, including the central nervous system, immune system and red blood cell lineage. We seek to leverage our academic collaborations and focus our preclinical and clinical research

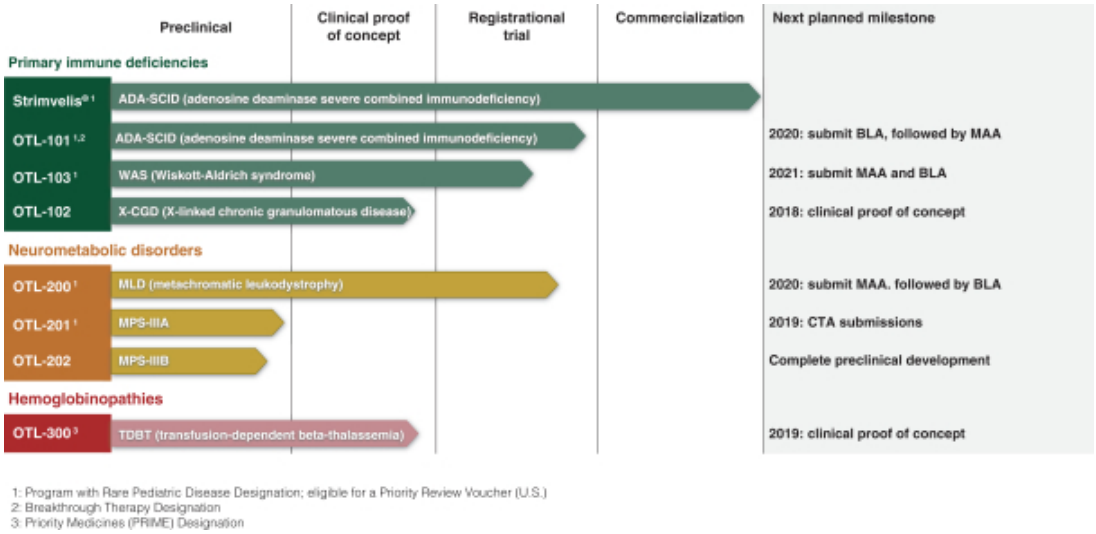
on rare disease indications with high unmet need and for which we believe there is a high probability of clinical success, based on the results observed in our clinical trials to date. For example, we are expanding our neurometabolic disorders franchise with the development of two preclinical programs, OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB. We anticipate submitting a CTA with the applicable regulatory authority in Europe for OTL-201 by the end of 2019 and plan to continue to progress preclinical development of OTL-202.

- **Establish an efficient and scalable manufacturing infrastructure:** The rare diseases we target affect patients around the world, and therefore we are building an infrastructure with the goal of delivering our gene therapies globally. To meet our near-term supply needs for initial commercialization primarily in the United States and Europe, we have established supply agreements with an international network of CMOs for vector manufacturing and for the production of drug product. We plan to invest in in-house manufacturing capabilities to accommodate our expanding process development and vector and drug product manufacturing activities and to continue building our international supply chain. We are also developing and implementing cryopreservation processes for our clinical-stage product candidates, which, in combination with our international network of CMOs and our planned in-house manufacturing capabilities, will help enable the distribution and administration of our gene therapies to wherever patients are located across the globe. In addition, we are investing in several initiatives to improve the efficiency of our manufacturing processes, including the automation of certain aspects of our production processes, with the goal of reducing production costs and our cost of goods. We are also executing on our plans for development of stable cell lines for OTL-102 and OTL-300. We believe that these initiatives will ultimately position us to deliver our gene therapy products efficiently and at a global scale commensurate with patient demand as our product offerings grow.
- **Establish a patient-centered, global commercial infrastructure:** We have global commercial rights to all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, subject to obtaining necessary marketing approvals. Leveraging the knowledge gained through our commercial product Strimvelis for ADA-SCID, and given our focus on rare genetic diseases, we plan to deploy a focused commercial infrastructure to deliver our product candidates to patients. In addition, we believe there is an urgent need to improve the early diagnosis of patients with rare genetic diseases, including those in our current focus areas, and we are implementing programs to improve patient and physician education regarding early access to transformative gene therapies for these conditions. We believe the value proposition for patients, caregivers, specialist physicians and payors is significant, given the potentially long-lasting benefits anticipated from our gene therapies. Accordingly, we are focused on working closely with all relevant stakeholders to ensure the widest possible post-approval access for our product candidates.
- **Execute a disciplined business development strategy to strengthen our portfolio of product candidates:** We have built our broad pipeline of product candidates through partnerships with leading academic institutions and through multiple successful in-licensing and acquisition deals. We will continue to evaluate new in-licensing opportunities and collaboration agreements with leading academic institutions and other biotechnology companies around programs that seek to address areas of high unmet need and for which we believe there is a high probability of clinical success, including programs beyond our target franchise areas and current technology footprint.

Our pipeline

Our advanced portfolio of autologous *ex vivo* gene therapies targets serious and life-threatening rare diseases, initially focusing on primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Over 150 patients have been treated as of September 2018 across our lead programs. Our primary immune deficiencies franchise consists of our commercial program, Strimvelis for ADA-SCID, two advanced registrational clinical programs, OTL-101 for ADA-SCID and OTL-103 for WAS, and one clinical-stage program, OTL-102 for X-CGD. Our neurometabolic disorders franchise consists of one advanced registrational clinical program, OTL-200 for MLD, and two preclinical programs, OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB. Our hemoglobinopathies franchise consists of one clinical-stage program, OTL-300 for TDBT.

The status of the lead pipeline programs is outlined below:



1: Program with Rare Pediatric Disease Designation; eligible for a Priority Review Voucher (U.S.)
2: Breakthrough Therapy Designation
3: Priority Medicines (PRIME) Designation

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare or ultra-rare indications, we believe our clinical programs will generally be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. For purposes of this prospectus, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial. See "—Our Regulatory Strategy."

Gene therapy treatment of ADA-SCID

Disease overview

Severe combined immunodeficiency, or SCID, is a rare, life-threatening inherited disease of the immune system. ADA-SCID, commonly known as "bubble-baby disease", is a specific form of SCID caused by mutations in the ADA gene, resulting in a lack of, or minimal, immune system

development, which leaves the patient vulnerable to severe and recurrent bacterial, viral and fungal infections. The first symptoms of ADA-SCID typically manifest during infancy with recurrent severe bacterial, viral and fungal infections and overall failure to thrive, and without treatment the condition can be fatal within the first two years of life. The lack of a functional ADA gene in ADA-SCID patients can also lead to neurological deficits involving motor function, deafness, hepatic dysfunction and eventual failure, and cognitive and behavioral dysfunction.

The incidence of ADA-SCID in the United States is currently estimated to be between one in 200,000 and one in 1 million live births. Higher incidence rates are reported in geographies of higher consanguinity, such as Turkey and the Middle-East.

Patients with ADA-SCID are most commonly diagnosed during the first six months of life based on recurrent bacterial, fungal, and viral infections, persistent lymphopenia, and ADA activity below 1%. Newborn screening for T-cell deficiencies, including ADA-SCID, has now been adopted in 49 states in the United States, as well as in Ontario, Israel, Taiwan and Norway.

Limitations of current therapies

The primary treatment options for ADA-SCID are HSCT and ERT. Although HSCT is a potentially curative treatment for ADA-SCID patients, this procedure is associated with a high risk of complications and mortality, with one-year survival rates of 43%, 67% and 86% for transplants from haploidentical donors, HLA-matched unrelated donors and HLA-matched sibling donors, respectively. HSCT also does not treat the cognitive and behavioral manifestations of ADA-SCID.

Chronic ERT is a palliative treatment for ADA-SCID patients and involves weekly or bi-weekly muscular infusions. ERT with pegylated adenosine deaminase has been approved by the FDA and is commercialized only in the United States. It is only available on an ad-hoc basis under compassionate use in Europe. Although ERT can temporarily restore immune function by maintaining high ADA levels in the plasma, many patients receiving chronic ERT therapy continue to have abnormally low levels of lymphocytes in the blood after the first year of treatment, and 50% of patients therefore require supplementary immunoglobulin replacement therapy. Chronic ERT is associated with a 78% survival rate at 20 years; however, significant morbidity or mortality may occur as early as one to three years after the first treatment. Patients on ERT may experience refractory hemolytic anemia, chronic pulmonary insufficiency, and lymphoproliferative disorders.

Our solutions, OTL-101 and Strimvelis for treatment of ADA-SCID

We are developing OTL-101 as an autologous *ex vivo* lentiviral gene therapy to sustainably treat patients with ADA-SCID through a single administration. OTL-101 is manufactured from HSCs isolated from the patient's own bone marrow or mobilized peripheral blood, and is modified to add a functional ADA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a mild conditioning regimen.

OTL-101 has been investigated in multiple clinical trials in the United States and Europe. As of September 2018, 61 patients have been treated with OTL-101 drug product, with a maximum follow-up of up to approximately 6.5 years post treatment. Based on our ongoing discussions with the FDA, we expect our BLA submission will include data from our UCLA registrational trial of 20 patients treated with a fresh product formulation, supportive data derived from at least five patients treated with a cryopreserved formulation at UCLA and additional data derived from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, as well as any other patients with adequate follow-up at the time of submission. See "—Regulatory Pathway

for OTL-101." The remaining 26 patients treated as of September 2018 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this prospectus but for which safety data is presented in the summary below. Among the 61 patients treated so far, three patients, including one patient in the supportive UCLA trial, one patient in the additional GOSH trial and one in the compassionate use program, did not engraft and had to resume enzyme replacement therapy and/or receive rescue bone marrow transplant.

In the European Union, our commercial program Strimvelis is available as the only approved gene therapy option for patients with ADA-SCID. The EMA approved Strimvelis in May 2016 for treatment of children with ADA-SCID with no suitable HLA-matched stem cell donor. Strimvelis consists of HSCs transduced with a gammaretroviral vector, an earlier generation of vector for autologous *ex vivo* gene therapy, encoding the human adenosine deaminase cDNA sequence. Strimvelis is available in fresh product formulation at San Raffaele Hospital in Milan, Italy, and has a shelf-life of up to six hours. We plan to continue to make Strimvelis available to eligible patients as we advance OTL-101 as an autologous *ex vivo* lentiviral gene therapy for ADA-SCID.

We obtained worldwide rights to the OTL-101 program through our license agreement with UCLB and UCLA and we obtained worldwide rights to the Strimvelis program through the GSK Agreement.

OTL-101 has received orphan drug designation from the FDA and the EMA for the treatment of ADA-SCID and Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA. We expect to submit a BLA for OTL-101 with the FDA in 2020, followed by an MAA submission with the EMA.

Ongoing registrational, supportive and additional clinical trials

OTL-101 has been evaluated in a registrational trial conducted by UCLA in the United States using a fresh product formulation and is being evaluated in an ongoing supportive clinical trial at UCLA using a cryopreserved formulation. These trials were initially conducted under an investigator-sponsored IND, which was subsequently transferred to us. A fresh product formulation is being evaluated in a concurrent additional investigator-sponsored clinical trial conducted by GOSH in Europe. Each of these clinical trials enrolled ADA-SCID patients between one month and 18 years of age who were ineligible for HSCT due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

Registrational trial at UCLA

Our anticipated rolling BLA submission for OTL-101 will include data from 20 enrolled and treated patients in a registrational trial at UCLA for which follow-up has recently completed. Production of the fresh OTL-101 drug product formulation (with bone marrow as the cellular source) used in this clinical trial was performed onsite at UCLA. In this clinical trial, all patients were treated with ERT prior to enrollment and continued ERT until 30 days following their initial treatment with OTL-101.

The primary goals of this clinical trial were to assess the safety and efficacy of OTL-101 in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial included immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates.

Overall survival and event-free survival of 100% was observed at 12 months post-treatment, the primary endpoint of the trial. None of the enrolled patients required rescue medication, HSCT, or resumption of ERT. Importantly, patients in this trial showed immune cell reconstitution

following treatment with OTL-101, which can lead to restoration of both cellular and humoral immune responses. This is reflected by the patients' ability to recover from infections beginning in the first six months following treatment. As of April 2017, the number of infections in evaluable patients decreased from 17 in the first year following treatment with OTL-101 to seven in the second year following treatment, and the number of serious infections in evaluable patients decreased from seven to one during the same period.

As summarized in the charts below, these patients' data were compared with a historical cohort of ADA-SCID patients, 0 to 18 years of age, who received treatment with allogeneic bone marrow transplant between 2000 and 2016 (n=26). These data were gathered retrospectively from Great Ormond Street Hospital and Duke University Hospital. Comparator populations from this group were ADA-SCID patients without a medically eligible HLA-matched sibling/family donor (HSCTWOUT), patients with an HLA-matched related donor (HSCTWITH) and the complete group (HSCTALL).

As summarized in the chart below, when comparing the overall survival for the OTL-101 treated patients with the historical control group, OTL-101 treated patients achieved higher overall survival rates at 12 months and 24 months (both at 100%) versus the combined group that received allogeneic bone marrow transplant 92.31% (95% CI: 75%-99%) at 12 months and 88% (95% CI: 69-97%) at 24 months. A confidence interval, or CI, is a range of values in which, statistically, there is a specified level of confidence that the true rate falls within this range. Small sample sizes will yield wider confidence intervals. In this trial, the results indicate that there is a 95% level of confidence that overall survival rates at 12 months were between 75% and 99%, which we represent as (95% CI: 75%-99%), and a 95% level of confidence that overall survival rates at 24 months were between 69% and 97%, which we represent as (95% CI: 69-97%).

OTL-101 (ADA-SCID): summary of Overall Survival (OS)

Overall Survival (OS) at 12 months (primary endpoint)

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	**100%** (83.16, 100)	-
HSCT without MRD	**85.71%** (57.19, 98.22)	**14.29%** (-5.40, 42.81)
HSCT with MRD	**100%** (73.54, 100)	-
All HSCT	**92.31%** (74.87, 99.05)	**7.69%** (-10.08, 25.13)

Overall Survival (OS) at 12 months

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	**100%** (78.20, 100)	-
HSCT without MRD	**85.71%** (57.19, 98.22)	**14.29%** (-8.99, 42.81)
HSCT with MRD	**90.91%** (58.72, 99.77)	**9.09%** (-14.24, 41.28)
All HSCT	**88%** (68.78, 97.45)	**12.00%** (-12.18, 31.56)

As summarized in the chart below, event-free survival is defined as survival without resumption of PEG-ADA enzyme replacement therapy or need for rescue allogeneic HSCT. Event-free survival in the OTL-101 treatment group was 100% at 12 months and at 24 months. In comparison, event-free survival in the combined allogeneic HSCT group was 80.77% (95% CI: 60.7-93.5%) at 12 months and 56% (95% CI: 34.9-75.6%) at 24 months. For the primary comparator group, who received allogeneic HSCT without a matched related donor, event-free survival rates were 35.71% lower (95% CI: 11.21-64.86%) and 50% lower (95% CI: 20.70-76.96%) than the OTL-101 treated group at 12 months and 24 months, respectively. Because the 95% confidence intervals for these estimates of the difference from the OTL-101 treated group do not include zero, these are statistically meaningful differences between the OTL-101 treated group and the HSCT without a matched related donor comparator group. Similarly, event-free survival in the comparator HSCT group that received a matched related donor (the current standard of care)

was 36.36% lower (95% CI: 7.31-69.21%) than the OTL-101 treated group at 24 months. Because the 95% confidence intervals for this estimate does not include zero, this also represents a statistically meaningful difference between the OTL-101 treated group and the comparator HSCT with a matched related donor.

OTL-101 (ADA-SCID): summary of Event Free-Survival (EFS)

Event Free Survival (EFS) at 12 months (primary endpoint)

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (83.16, 100)	-
HSCT without MRD	64.29% (35.14, 87.24)	35.71% (11.21, 64.86)
HSCT with MRD	100% (73.54, 100)	-
All HSCT	80.77% (60.65, 93.45)	19.23% (0.71, 39.35)

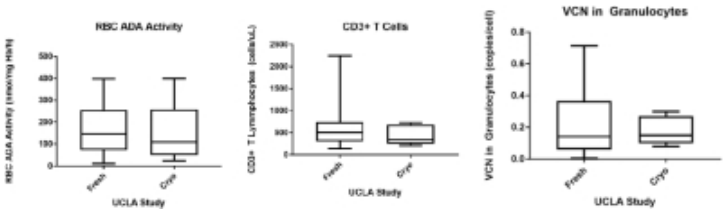
Event Free Survival (EFS) at 24 months

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (78.20, 100)	-
HSCT without MRD	50% (23.04, 76.96)	50% (20.70, 76.96)
HSCT with MRD	63.64% (30.79, 89.07)	36.36% (7.31, 69.21)
All HSCT	56% (34.93, 75.60)	44% (16.15, 65.07)

Ongoing supportive clinical trial with UCLA (with cryopreserved formulation)

A cryopreserved formulation of OTL-101 (with bone marrow as cellular source) is currently being evaluated in an ongoing supportive clinical trial at UCLA. Enrollment for this trial is complete; 10 patients have been treated, with currently available follow-up data of between 2.9 months to 9.3 months, as of January 2018. One patient treated in this trial did not engraft and had to resume enzyme replacement therapy and/or receive rescue bone marrow transplant. The aim of this clinical trial is to assess the success of treatment at the patient level, referred to as a responder analysis, at six-months post-treatment, using predictive criteria for overall survival and event free survival.

In this trial, ADA activity, vector copy number, or VCN, and CD3+ T-cell counts at six months post-treatment are measured as key biological correlates of efficacy and compared with the results obtained from our registrational trial with fresh product formulation. We expect to use these data to support the analytical comparability analysis between fresh and cryopreserved formulations that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively. Data from the first five patients that successfully engrafted and achieved the six month post-treatment follow-up date shows similarity in these biological correlates of efficacy measured in patients from the UCLA fresh trial (n=10) at 6 months. We believe this consistency between the UCLA fresh and cryopreserved studies is supportive of ongoing analytical comparability data between the fresh and cryopreserved formulations of OTL-101. We are continuing to evaluate the data from this ongoing trial and will include the data available at the time of submission to support our BLA and MAA submissions.



RBC = red blood cells; ADA = adenosine deaminase; VCN = vector copy number. The figure shows data for UCLA Fresh trial patients (“Fresh”, n = 20) and UCLA Cryo trial with 5 evaluable patients (“Cryo”, n = 5) at 6 months of follow-up The boxes indicate the median and inter-quartile range, the ‘whiskers’ are the minimum and maximum values for each group.

Additional clinical data from GOSH

In a parallel investigator-sponsored trial being conducted by GOSH, 10 enrolled patients have been treated with fresh product formulation (with bone marrow and mobilized peripheral blood as the cellular source). The drug product used in this clinical trial is produced using the same vector as at UCLA but with a manufacturing process with minor differences to that for OTL-101. Production of the fresh formulation of the drug product used in this clinical trial was performed onsite at GOSH. In this clinical trial, all patients were being treated with ERT prior to enrollment and all but one patient continued ERT until 30 days following initial treatment with autologous *ex vivo* HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates.

As of September 2017, overall survival of 100% has been observed at 12 months post treatment in the 10 patients enrolled, and nine patients have achieved event-free survival, with only one patient resuming ERT after 12.2 months due to a failure to engraft. We believe this failure to engraft may in part be attributable to the patient's early discontinuation of ERT prior to treatment in contravention of the trial protocol, but may also relate to other clinical factors.

Importantly, patients in this trial showed immune reconstitution following treatment with the drug product, which can lead to restoration of both cellular and humoral immune responses. This is reflected by the patients' ability to recover from infections beginning in the first six months following treatment. As of March 2017, the number of infections in evaluable patients decreased from 16 in the first year following treatment to two in each of the second and third years following treatment, and the number of serious infections in evaluable patients decreased from two in the first year following treatment to zero and one in the second and third years, respectively.

There is a second investigator-sponsored trial being conducted by GOSH, aiming to enroll 10 patients treated with cryopreserved product formulation with mobilized peripheral blood as the cellular source. The drug product used in this clinical trial is produced using the same vector and same manufacturing process as the drug product being evaluated at UCLA. Production of the cryopreserved formulation of the drug product used in this clinical trial is performed onsite at GOSH. In this clinical trial, all patients are being treated with ERT prior to enrollment and continue ERT until 30 days following initial treatment with autologous ex vivo HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates. As of September 14, 2018, five patients have been treated and are alive and off of ERT.

OTL-101 Program Safety

As of September 2018, safety data from the 20 patients treated in the registrational trial in the United States indicate that OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis in follow-ups ranging from 19.2 months to 33 months. There were 51 SAEs reported, 14 of which were assessed by the investigator as being possibly related to protocol treatment or procedures. One of these SAEs was a staphylococcal infection from the transduced bone marrow cells. The patient was treated with antibiotics and recovered. The most common SAEs were

pyrexia, infections and gastrointestinal disorders. There were no adverse events, or AEs, or SAEs leading to the withdrawal of patients from the trial. All SAEs resolved with standard of care treatment. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR.

As of September 2018, safety data from the 10 patients treated in the supportive clinical trial with UCLA in the United States and from the two compassionate use patients receiving a cryopreserved formulation, indicate OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis up to 1.5 years post treatment. There were 14 SAEs reported in the UCLA supportive clinical trial, three of which (two events of leukopenia and one event of neutropenia in the same patient) were assessed by the investigator as being related to the protocol treatment or procedures and were the result of the patient's failure to achieve engraftment. In the compassionate use program, 5 SAEs were reported and were not deemed to be related to OTL-101. The most common SAEs across the UCLA supportive clinical and United States compassionate use program were leukopenia, pyrexia, and infections. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR.

In Europe, as of September 2018, safety data from the 10 patients treated in the additional clinical trial with GOSH and from the 10 compassionate use patients, indicate that the investigational drug product was generally well-tolerated, with no instances of insertional mutagenesis up to six years post treatment. There were 25 SAEs reported in the additional clinical trial with GOSH, none of which were assessed by the investigator as being possible related to the protocol treatment or procedures, and six SAEs reported in the compassionate use program, one of which, a product contamination, was deemed by the investigator as being possibly related to protocol treatment or procedures. This SAE was a staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. The most common SAEs across the additional clinical trial and compassionate use program were pyrexia, infections and immune system disorders. There were no AEs or SAEs leading to the withdrawal of patients from the additional clinical trial and compassionate use program. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR. In a cryopreserved study protocol in the United Kingdom, where five of ten patients have been recently treated, there were two SAEs reported, neither of which were deemed to be related to the drug product. In three patients treated under compassionate use with cryopreserved formulation, nine SAEs have been reported, none of which were deemed to be related to the product.

Regulatory Pathway for OTL-101

We are currently in discussions with the FDA to finalize the requirements for our planned BLA submission for OTL-101 in 2020. Based on these discussions, we currently expect that our BLA submission will include clinical data from a registrational trial of 20 patients treated with a fresh product formulation at UCLA, supportive data derived from at least five patients treated with a cryopreserved formulation at UCLA, additional data from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, and any other patients with adequate follow-up at the time of submission. Prior to completion of our BLA submission for OTL-101, we will be required to prepare a final clinical trial report for our registrational trial, as well as our supportive clinical trial to support the analytical comparability data between fresh and cryopreserved drug product formulations. We expect to have further discussion with FDA regarding our CMC data package.

Ultimately, the FDA will determine whether or the extent to which those data may be included in an application for marketing approval or even if included, the extent such data is considered for assessment of quality, safety, efficacy of the drug product candidate. We expect to have an additional CMC-focused meeting with the FDA prior to our BLA submission to discuss analytical comparability between academic and commercial manufacturing processes, vector and drug product process characterization and process validation approach, including demonstration of manufacturing state of control. We also plan to discuss with the FDA the data required for the inclusion of patients' mobilized peripheral blood as the cellular source material, together with patient bone marrow, in the label for OTL-101, if approved. Pending the outcome of these discussions, we may elect to initially seek approval of OTL-101 using patient bone marrow and subsequently seek approval for the use of mobilized peripheral blood. Although we currently expect to submit our BLA by 2020, our discussions with FDA are ongoing and we do not yet have definitive feedback from the FDA on the scope or adequacy of the requisite data necessary to support an approval and additional analytical comparability or clinical data may be required. See "Risk factors – The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates," "Risk factors – We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product" and "Risk factors – To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites."

Gene therapy for treatment of MLD

Disease overview

MLD is a rare and rapidly progressive neurometabolic disorder. MLD is caused by a mutation in the ARSA gene, leading to a deficiency in the ARSA enzyme and the accumulation of sulfatides and the progressive destruction in myelin-forming neurons in central and peripheral nervous systems and in visceral organs. Prognosis is severe, with continuous neurodegeneration and rapid deterioration of motor functions and cognitive impairment. In late-infantile MLD, the most common and severe form of the disease representing approximately 40-60% of all MLD patients, symptoms are generally first observed before three years of age, and the rate of mortality by five years of age is estimated at 50%. In juvenile MLD, representing approximately 20-35% of all MLD patients, symptoms are generally first observed between three and 16 years of age, and the rate of mortality at ten years of age is estimated at 44%. In adult MLD, representing approximately 10-25% of all MLD patients, the onset of symptoms generally occurs after 16 years of age. Prognosis is severe, with continuous neurodegeneration and rapid progression of motor and cognitive impairment. Symptoms often manifest in late-infantile and early-juvenile MLD patients as incorrect gait and missed development milestones. Adult-onset MLD is often diagnosed through cognitive, behavioral and psychiatric pathologies, such as alcohol or drug use, or difficulty managing emotions resulting in psychiatric evaluation. MLD patients may also demonstrate bewilderment, inappropriate response to their surroundings, paranoia, dementia or auditory hallucinations.

The incidence of MLD is currently estimated at between 1.4 in 100,000 and 1.8 in 100,000 live births per year.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MLD. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well

as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MLD but does not slow or reverse the progression of the underlying disease. HSCT has limited and variable efficacy in arresting disease progression and, as a result, HSCT is not considered to be a standard of care for this disease. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MLD patients, their caregivers and families and healthcare systems.

Our solution, OTL-200 for treatment of MLD

We are developing OTL-200 as an autologous *ex vivo* lentiviral gene therapy to sustainably treat patients with MLD through a single administration. OTL-200 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood or bone marrow, modified to add a functional ARSA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen. The gene-modified HSCs have the capacity to migrate to the brain, differentiate into microglia in the brain tissue and secrete the ARSA enzyme to treat the disease within the central nervous system.

To date, we have treated only late infantile and early juvenile patients in our clinical trials of OTL-200. As of September 2018, a total of 31 patients have been treated with OTL-200 drug product, with a maximum follow-up of up to approximately eight years post treatment, comprised of 20 patients in our registrational trial with a fresh product formulation, two patients in our supportive study with a cryopreserved formulation and nine patients treated under a compassionate use program with a fresh product formulation. Based on our clinical data to date, we believe OTL-200 has shown the potential to maintain motor function and intelligence quotient, or IQ, in patients.

We obtained worldwide rights to this program through the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored CTA, which we expect will be transferred to us by the end of 2018.

OTL-200 has received orphan drug designation from the FDA and the EMA for the treatment of MLD. OTL-200 has also received Rare Pediatric Disease Designation from the FDA. We plan to submit an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA.

Registrational trial

Our anticipated MAA and BLA submissions for OTL-200 will be supported by data from 20 patients with pre-symptomatic late infantile MLD, or pre- to early-symptomatic early juvenile MLD, currently enrolled and treated in a registrational trial at San Raffaele Hospital in Milan, Italy, for which follow-up is ongoing. In this registrational trial, all patients have achieved the primary endpoint at 24 months follow-up. In addition to the 20 patients treated with OTL-200 in this clinical trial, nine patients were treated under compassionate use programs at San Raffaele Hospital, which followed the same protocol as that used in the clinical trial. Manufacture of the fresh OTL-200 drug product formulation (with bone marrow as cellular source) was performed by a third-party commercial CMO.

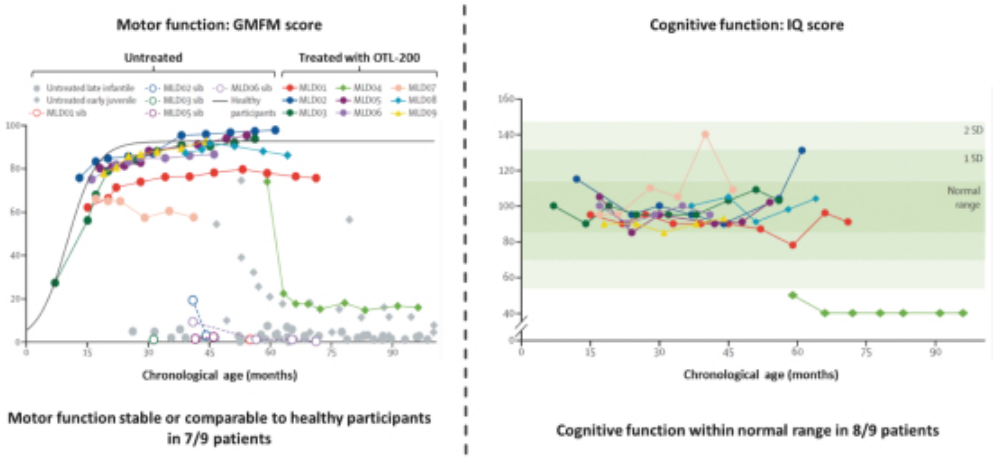
The primary goals of this clinical trial were to assess the efficacy and safety of OTL-200 in MLD patients, as measured by gross motor function and ARSA activity levels in the patients' blood cells 24 months post-treatment, as well as overall survival. Secondary goals for this clinical trial included assessment of cognitive function through IQ. The trial also provides for a follow-up period ending at 36 months' post-treatment.

Interim data from an ad hoc analysis of the first nine patients in this registrational trial was published in *Lancet Neurology* in 2016 and is set forth below. For purposes of this analysis, these interim data were presented in contrast to data from a historical cohort of 21 patients with late-infantile MLD and nine patients with early-juvenile MLD who had not received treatment, and to

data from a cohort of 34 healthy children. Of the nine patients treated with OTL-200, six had late-infantile disease, two had early-juvenile disease and one had early-onset disease that could not be definitively classified.

In this interim analysis, eight patients treated with OTL-200, seven of whom received treatment when pre-symptomatic, had prevention of disease onset or halted disease progression, as compared with patients in the natural history group, most of whom experienced rapid disease progression. In addition, the gross motor function measure score, or GMFM score, for six patients up to the last follow-up showed that gross motor performance was similar to that of normally developing children. Neurocognitive development as measured by IQ score was within the normal range for eight patients, as compared to the natural course of the disease in untreated patients with early-onset MLD (data not shown in the publication). Also, IQ values of untreated patients all fell below the minimum value of 40 since first available testing (data not shown in the publication).

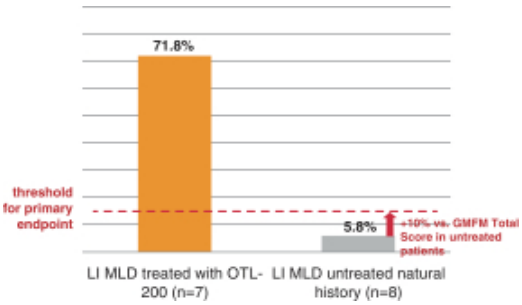
OTL-200 (MLD): Demonstrated Clinical Benefit for Motor and Cognitive Function



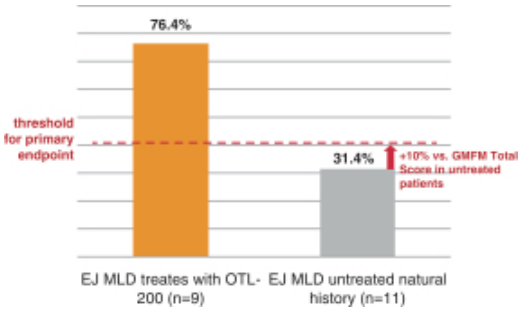
Presented below are efficacy data from a more recent interim analysis of all 20 patients treated in this clinical trial as of December 2017, the date of the most recent interim efficacy data report available to us. Motor function was measured in this trial with a GMFM score, which measures a child's ability to perform standard motor tasks including lying and rolling, sitting, crawling and kneeling, standing, and walking, and running and jumping. A GMFM score of approximately 100% is representative of an individual with normal motor function. Following treatment with OTL-200, preliminary data indicate GMFM scores comparable to healthy individuals in seven out of nine late infantile patients, with a follow-up of up to three years. This primary endpoint was deemed to be achieved if there was a 10 percentage point improvement in GMFM scores compared to the untreated MLD natural history population at 24 months. Improvement in motor function has been observed in patients treated with OTL-200 compared to natural history patient data. At 24 months post-treatment, an average GMFM score of 71.8% was observed in late infantile patients (n=9) treated in this clinical trial compared to 5.8% in the untreated natural history population. For early juvenile patients treated in this clinical trial (n=11), an average GMFM score of 76.4% was observed at 24 months post-treatment, compared to 31.5% in the natural history population.

OTL-200 (MLD): GMFM Total Score

GMFM Total Score in late infantile MLD at 24 months post OTL-200 vs. natural history



GMFM Total Score in early juvenile MLD at 24 months post OTL-200 vs. natural history



In addition, OTL-200 evidenced increases in ARSA levels in most patients to within the normal range, as measured at three months post-treatment, achieving levels that fluctuated within or above the normal range throughout the duration of the follow-up. This co-primary endpoint was deemed to be achieved if ARSA values exceeded two standard deviations from baseline. Sustained ARSA levels well above two standard deviations post-treatment were observed in all patients in this trial.

Cognitive function in patients treated with OTL-200 has been measured using the IQ score. The stability or deterioration of a patient's cognitive abilities were monitored using the neuropsychological tests administered according to the chronological age of the patient. Each neuropsychological instrument includes multiple core tests and supplemental subtests that comprise composite scores in specified cognitive areas. Following treatment with OTL-200, seven of the nine (78%) late infantile patients remained within normal ranges and seven of the eleven (64%) early juvenile patients had an IQ either within, close to or above the normal range.

As of March 2018, the date of the most recent safety report available to us, overall survival has been observed in 18 of 20 patients enrolled in the study, with a maximum follow-up of up to approximately 7.5 years and a median follow-up of approximately 4 years. Two patients with early juvenile MLD that were symptomatic at the time of treatment died from advanced disease progression that was deemed to be unrelated to the treatment by the investigator. From the 20

patients treated in the clinical trial indicate OTL-200 was generally well-tolerated, with no instances of insertional mutagenesis up to eight years post-treatment. 31 SAEs were reported in the patients in the clinical trial, none of which were assessed by the investigator to be related to OTL-200. In addition, as of March 2018, nine patients were treated under compassionate use, all of whom are alive; six SAEs were reported, none of which were assessed by the investigator to be related to the drug product. Across the program, the most common SAEs were motor dysfunction, dysphagia, vomiting and infections. There were no OTL-200 related SAEs. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in the clinical trial of any SUSAR.

Ongoing cryopreservation supportive clinical trial

A cryopreserved formulation of OTL-200 (with bone marrow as cellular source) is currently being evaluated in an ongoing clinical trial of pediatric patients with pre-symptomatic early onset MLD in Milan, Italy. Enrollment for this trial is ongoing, with two patients enrolled as of September 2018 and up to 10 patients expected to be enrolled.

The primary goal of this clinical trial is to assess the safety and efficacy of a cryopreserved formulation of OTL-200 in MLD patients, as measured by improvement in gross motor function and ARSA activity levels in the patients' blood cells as well as overall survival. Secondary goals for this clinical trial include assessment of cognitive function through IQ.

The first patient in this trial was treated in March 2018, and as of July 2018, the patient tolerated the administration well and has shown evidence of engraftment with supranormal production of ARSA.

We expect to use these clinical data to support the analytical comparability analyses between fresh and cryopreserved formulations that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively.

Regulatory Pathway for OTL-200

We are currently in discussions with the EMA to finalize the requirements for our planned MAA submission for OTL-200 in 2020. Based on these discussions, we currently expect that our MAA submission will include clinical data from a registrational trial of 20 late infantile and early juvenile MLD patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as any other patients with adequate follow-up at the time of submission, treated with a fresh product formulation under compassionate use. Prior to completion of our MAA for OTL-200, we will be required to prepare a clinical trial report for our registrational trial, as well as our supportive clinical trial with cryopreserved formulation to support analytical comparability between fresh and cryopreserved drug product formulations. We expect to have a follow-up scientific advice and a pre-MAA meeting with the EMA to discuss the targeted label, last elements of comparability between fresh and cryopreserved formulations manufacturing processes as well as between drug product manufactured using HSCs derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow. A paediatric investigational plan compliance check will also need to be completed. Although we currently expect to complete our MAA submission in 2020, our discussions with EMA are ongoing and we do not yet have definitive feedback from the EMA

on the scope or adequacy of the requisite data necessary to justify an approval. See “Risk factors—The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates,” and “Risk factors—We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

Gene therapy for treatment of WAS

Disease overview

WAS is a rare, life-threatening inherited disease affecting the patient’s immune system and platelets leading to recurrent, severe infections and uncontrollable bleeds, which are the leading causes of death in the disease. WAS is referred to as an “X-linked-recessive” disease as it is associated with a genetic defect on the X chromosome. Because it is an X-linked disease, it affects mainly males. Patients with WAS are born with a defect in the gene that produces the WAS protein, or WASP. As a result, they suffer from life-threatening thrombocytopenia and are at risk of severe bleeds, infections, autoimmunity, malignancies and severe eczema. These symptoms require increasingly frequent hospitalizations. The median survival for a patient with WAS is approximately 15 years with patients with early onset WAS generally having a shorter life expectancy.

The incidence of WAS is currently estimated at approximately four in 1 million live male births.

Limitations of current therapies

Treatment options for WAS include conservative care with prophylactic anti-infective medicines, which are not always effective in preventing severe infections requiring antibiotics, antivirals, antifungals and intravenous immunoglobulin, as well as chronic platelet transfusions to prevent severe bleeding. WAS patients often are prescribed chronic oral medications or topical steroids and may require admission to hospital for intravenous antibiotic treatment. HSCT is an alternative treatment option for some patients for whom a sufficiently well-matched donor is identified. Although HSCT is potentially curative in patients with WAS, this approach can be associated with significant risks, especially when perfectly-matched cell donors are not available. Approximately 75% of WAS patients treated with HSCT experience serious complications, such as severe infections requiring hospitalization, autoimmune manifestations, and GvHD, within the first year of receiving the treatment.

Our solution, OTL-103 for treatment of WAS

We are developing OTL-103 as an autologous *ex vivo* lentiviral gene therapy to treat patients with WAS through a single administration. OTL-103 is manufactured from HSCs isolated from the patient’s peripheral blood or bone marrow that are modified to add a functional WASP gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a milder conditioning regimen compared to HSCT.

As of September 2018, eight patients have been treated with OTL-103 in an ongoing registrational trial and eight patients in a compassionate use program, with a maximum follow-up of up to approximately eight years post-treatment.

We obtained worldwide rights to this program through the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored CTA, which was transferred to us in August 2018.

OTL-103 has received orphan drug designation from the FDA and the EMA for the treatment of WAS. OTL-103 has also received a Rare Pediatric Disease Designation from the FDA. We plan to submit an MAA with the EMA and a BLA with the FDA for our OTL-103 for the treatment of WAS in 2021.

Registrational trial

Our anticipated MAA and BLA submissions for OTL-103 will include data from eight currently enrolled patients treated with a fresh product formulation in a registrational trial at San Raffaele Hospital for which follow-up is ongoing. The primary analysis for this registrational trial is prospectively defined to be when all patients have completed three years' follow-up. The eighth and final patient in this trial is expected to reach three years' follow-up by the end of September 2018. Manufacture of the fresh OTL-103 drug product formulation (with bone marrow or mobilized peripheral blood as the cellular source) was performed by a third-party commercial CMO. Data from the registrational trial will be supported by eight patients dosed in a compassionate use program. Based on discussions with the EMA, we intend to submit data to the EMA from additional patients treated with a cryopreserved formulation.

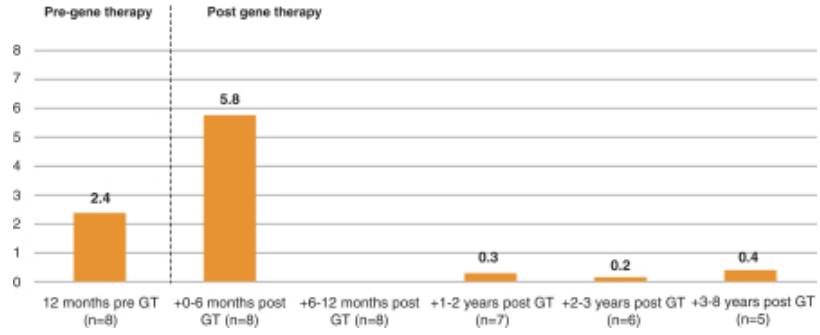
Patients treated in the registrational trial and compassionate use program were below the age of 12 years with a diagnosis of severe, classical WAS and were ineligible for HSCT treatment due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

The primary goals of this clinical trial are to assess the efficacy and safety of OTL-103 in WAS patients, as measured by, for example, improved T-cell function, improved platelet count and overall survival at 36 months. Secondary goals of this clinical trial include reduced bleeding episodes and reduced frequency of infections.

As of April 2016, the date of the most recent interim data report available to us, WASP expression in lymphocytes and platelets was substantially improved compared to baseline by six months and remain constant thereafter. At one year post-treatment with OTL-103, T-cell counts increased in all seven evaluable patients, as compared to counts prior to treatment, reaching normal values. Because of the increase in T-cells, a reduction in infections was observed in patients post-treatment compared to one year prior to treatment with OTL-103.

OTL-103 (WAS): reduced frequency of severe infections

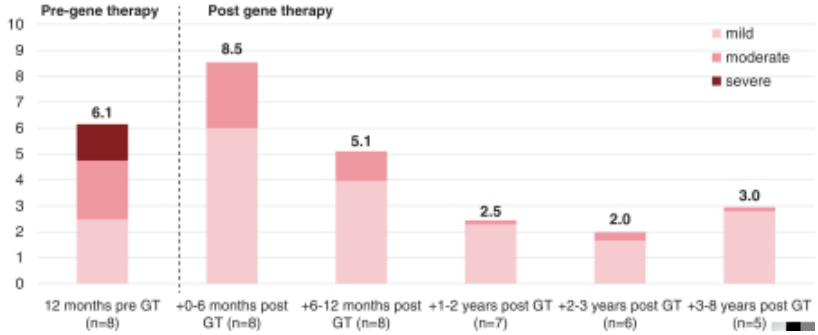
Severe infections per person/year



Mean platelet counts before treatment were low, with a range of 6–25 x 10^9 per liter observed in all eight patients. Platelet counts progressively improved in all patients. One year post-treatment platelet counts increased in all patients to a range of 21–74 x 10^9 per liter, and further increases in platelet count were observed in six patients to a range of 27–169 x 10^9 per liter at three years post-treatment. In addition to the increase in platelet count, increased and sustained platelet volume in seven patients was also observed at three years post-treatment. These increases in platelet count and volume resulted in reduced frequency and severity of bleeding events as compared to those experienced by these patients prior to treatment with OTL-103 as shown in the graph below.

OTL-103 (WAS): reduced frequency and severity of bleedings

Bleedings per person/year



As of March 2018, the date of the most recent safety report available to us, 100% overall survival has been observed in the eight patients treated in the clinical trial, with a maximum follow-up of up to 7.8 years and a median follow-up of 5.7 years. Safety data from the eight patients treated in this registrational clinical trial indicate OTL-103 was well-tolerated, with no instances of insertional mutagenesis. There were 29 SAEs reported within the trial, none of which were assessed by the investigator as being related to OTL-103. Five SAEs were reported in seven patients treated under compassionate use, none of which were assessed by the investigator as being related to OTL-103. One of these compassionate use patients died as a consequence of a pre-existing neurological disease. That event was deemed to be unrelated to the product. The remaining six compassionate use patients are alive. Across the program, the most common SAEs were pyrexia, infections, electrolyte imbalance, food allergy and neutropenia. There were no OTL-103 related SAEs leading to the withdrawal of patients from the trial. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR.

Regulatory Pathway for OTL-103

We are currently in discussions with EMA and FDA to finalize the requirements for our planned MAA and BLA submissions, respectively, for OTL-103 in 2021. We currently expect that our MAA and BLA submissions will include clinical data from a registrational trial of 8 patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as additional patients with adequate follow-up at the time of submission, treated with a fresh product formulation under compassionate use. In addition, prior to completion of our MAA and BLA for OTL-103, we will need to collect clinical data with a cryopreserved formulation. We

will also be required to prepare a clinical trial report for our registrational trial, as well as our supportive clinical trial with cryopreserved formulation to support analytical comparability between fresh and cryopreserved drug product formulations. We expect to have meetings with EMA and FDA, including a pre-MAA and a pre-BLA meeting, to obtain their concurrence on the appropriate data to support our marketing authorization application. Although we currently expect to complete our MAA and BLA submission by 2021, our discussions with EMA and FDA are ongoing and we do not yet have definitive feedback from the EMA and FDA on the scope or adequacy of the requisite data necessary to justify an approval. See “Risk factors – The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates,” and “Risk factors – We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

Gene therapy for X-CGD

Disease overview

X-CGD is a rare, life-threatening inherited disease of the immune system. X-CGD is an X-linked-recessive disease and therefore affects males. Because of the underlying genetic defect in the cytochrome B-245 beta chain, or CYBB, gene in patients with X-CGD, the patient’s white blood cells, specifically neutrophils/granulocytes, are unable to kill bacteria and fungi, leading to repeated chronic infections. The main clinical manifestations of X-CGD are pyoderma; pneumonia; colitis; lymphadenitis; brain, lung and liver abscesses; and osteomyelitis. Granuloma formation can also occur as a result of persistent inflammatory response to the pathogens and can result in recurrent obstructions of the gastro-intestinal and urinary tract. Patients with X-CGD typically start to develop infections in the first decade of life. Mortality in X-CGD has been estimated at approximately 40% by the age of 35 years.

The incidence of X-CGD is currently estimated to be between 2.6 in 1 million and 10 in 1 million male live births.

Limitations of current therapies

Current treatment options for X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma, which are not always effective in preventing severe infections. Although HSCT is potentially curative in patients with X-CGD, this approach can be associated with significant risks, especially when well-matched cell donors are not available.

Our solution, OTL-102 for treatment of X-CGD

We are developing OTL-102 as an autologous *ex vivo* lentiviral gene therapy to treat patients with X-CGD through a single administration. OTL-102 is manufactured from HSCs isolated from the patient’s own mobilized peripheral blood or bone marrow, then modified to add a functional CYBB gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen.

OTL-102 is currently being investigated in ongoing investigator-sponsored clinical trials in the United States and in Europe and has evidenced sustained CYBB expression for over one year in four patients to date, with a follow-up for over two years post-treatment in the first successfully treated patient.

We obtained worldwide rights to the OTL-102 program through an option and license agreement with Généthon, pursuant to which we have exercised an option to certain intellectual property and clinical data associated with clinical trials sponsored by Généthon at sites in the United States and the United Kingdom and we continue to have the right to exercise an exclusive option with respect to an ongoing clinical trial conducted in France, which option expires in June 2019.

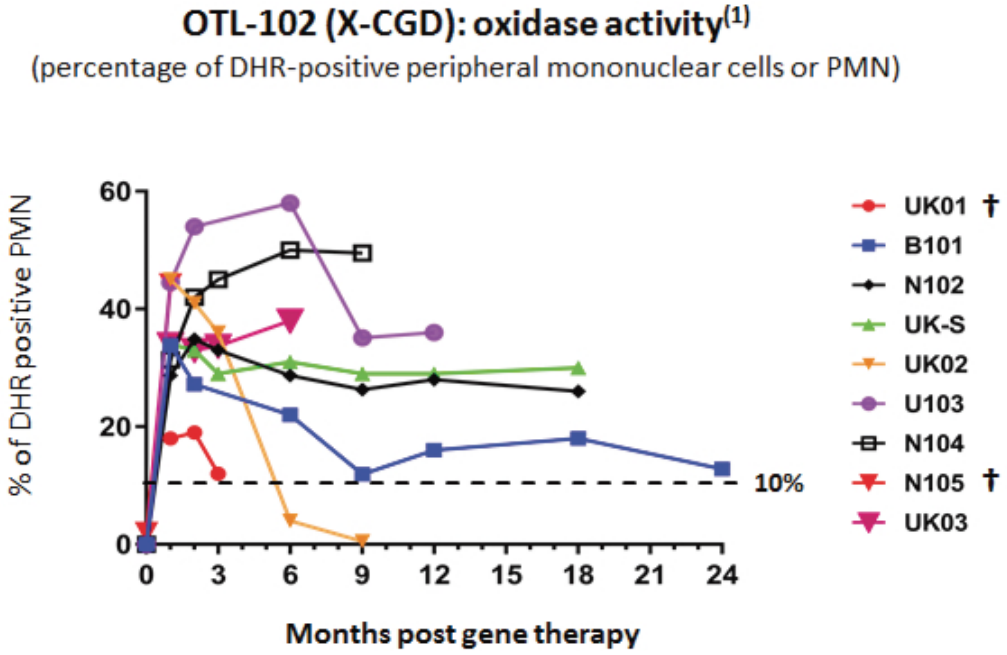
OTL-102 has received orphan drug designation from the EMA for the treatment of X-CGD.

Ongoing clinical trials

OTL-102 is currently being investigated in two ongoing investigator-sponsored proof of concept clinical trials in the United States and in Europe, with target enrollment of 10 patients in a clinical trial conducted by UCLA in the United States and target enrollment of five patients in a clinical trial conducted by GOSH in Europe. The clinical trial sites include Boston Children's Hospital, the NIH, and UCLA in the United States, and GOSH and The Royal Free Hospital in London. Manufacture of the drug product occurred at each of these sites using the same vector. As of January 2018, five patients have been treated in the clinical trial in the United States four of which were treated with a fresh product formulation and one of which was treated with a cryopreseved formulation, and three patients have been treated in the clinical trial in Europe, one of which was treated with a fresh product formulation and two of which were treated with a cryopreserved product formulation. Two patients have been treated in a compassionate use program in Europe, one with a fresh product formulation and the other with a cryopreserved product formulation. In the future, we expect to treat additional patients in this trial with a cryopreserved formulation of OTL-102. Patients enrolled in these trials have advanced and severe stages of X-CGD.

The primary goals of these clinical trials are to assess safety and efficacy, as measured by biochemical and functional reconstitution through increased nicotinamide adenine dinucleotide phosphate-oxidase, or NADPH, activity in progeny of engrafted cells and stability at 12 months post-treatment.

In these clinical trials, the production of NADPH activity in neutrophils, a biomarker that demonstrates restored granulocyte function, has been measured in patients for up to 24 months post-treatment. As of July 2018, preliminary combined data from the U.S. and U.K. studies, including the compassionate use patients, showed NADPH activity, as measured by dihydrorhodamine, or DHR, assay, above 10% in six patients with at least six months follow-up. Based on the investigator's review of the scientific literature, they determined that 10% was a clinically meaningful percentage for fighting infections successfully. The graphic below illustrates sustained NADPH levels, as measured for up to 24 months post-treatment.



(1) Excludes data from one patient treated with drug product deemed by the investigator to be a different from OTL-102 drug product.
† Patient deceased from advanced disease.

As of July 2018, the date of the most recent safety data available to us, safety data from the U.S. patients treated in this clinical trial indicate OTL-102 was generally well-tolerated, with no instances of insertional mutagenesis up to eight months post-treatment. There were eight SAEs reported, none of which were assessed by the investigator as being possibly related to drug product. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All AEs and SAEs resolved with standard of care treatment.

Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR. In the U.K. study, eight SAEs were also reported, one of which was deemed as possibly related to the product. This event is still under investigation by the data safety monitoring board.

Two of the nine patients treated with OTL-102 in these clinical trials died during the three months period following treatment as a result of pre-existing disease-related complications

present at the time of treatment with OTL-102. One patient from the U.K. trial died of acute respiratory distress syndrome. This subject had a pre-existing lung condition. One patient from the U.S. trial developed platelet antibodies due to sensitization after several granulocytes infusions the patient received prior to gene therapy. As a result, following gene therapy he was unable to respond to platelet transfusion and died from hemorrhage. Following this event, in September 2017, the investigators put this trial on hold, and after discussions with the FDA and the data safety monitoring board, the trial was re-initiated in February 2018. The learnings from this patient resulted in a protocol amendment to prevent patients with existing platelet antibodies from enrolling in the trial. Neither of these two fatalities was deemed by the investigator to be related to the therapy. A third fatality was reported involving a patient treated under the compassionate use program at GOSH. Because of this patient's advanced disease stage at the time of enrollment, the patient required a surgical procedure following treatment and died as a result of complications from this procedure. This fatality was deemed by the investigator not to be related to the product. This patient was treated with drug product manufactured under a different manufacturing process than that used for OTL-102, which was deemed by the investigator to be a different drug product than OTL-102, and therefore, this patient's data have been excluded from the data set in these clinical trials.

Gene therapy for treatment of TDBT

Disease overview

Beta-thalassemia is an inherited blood disorder caused by one of over 200 mutations in the hemoglobin beta, or HBB, gene. Patients with beta-thalassemia have low levels of hemoglobin, a protein in red blood cells that carries oxygen to cells throughout the body. TDBT is the most severe form of beta-thalassemia, and requires patients to receive eight or more blood transfusions per year, with the number of transfusions dependent upon the severity of the patient's disease. Symptoms in TDBT patients appear within the first two years of life and include failure to thrive, persistent infections and life-threatening anaemia. Patients with TDBT also suffer from other symptoms such as liver and spleen enlargement, bone deformities and osteopenia, and hypermetabolic state, resulting in chronic malnourishment. Patients often need a multidisciplinary team of cardiologist, hepatologist, endocrinologist, orthopedic, and psychologist support. In the absence of regular blood transfusions, TDBT is usually fatal in infancy.

TDBT is one of the most common genetic diseases, with a global incidence estimated at approximately 25,000 symptomatic individuals born each year.

Limitations of current therapies

The symptoms experienced by most patients with TDBT are severe and often require frequent, life-long blood transfusions to replenish the patient's hemoglobin level. Because iron cannot be excreted by the body, these frequent blood transfusions can cause iron to accumulate in various organs, leading to risk of heart or liver failure. Therefore, patients who receive ongoing blood transfusions must also receive iron chelation therapy to remove the excess iron. These medicines also have side effects and can negatively impact a patient's quality of life. Although HSCT is potentially curative in patients with TDBT, this approach can be associated with significant risks, especially when perfectly-matched cell donors are not available.

Our solution, OTL-300 for treatment of TDBT

We are developing OTL-300 as an autologous *ex vivo* gene therapy to sustainably treat patients with TDBT through a single administration. OTL-300 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood, then modified to add a functional HBB gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intra-osseous administration following treatment with a myeloablative conditioning regimen. We plan to investigate treatment through an intravenous administration of OTL-300 as part of the clinical development of this product candidate. OTL-300 is designed to significantly reduce or eliminate the need for blood transfusions in patients with TDBT.

As April 2018, OTL-300 has been evaluated in a total of nine patients, the majority of which have a severe genotype of TDBT, including ß0/ß0, in an ongoing clinical trial at San Raffaele Hospital in Milan, Italy, with follow-up of up to approximately three years. The clinical trials for this program are being conducted under an investigator-sponsored CTA.

We obtained worldwide rights to this program through the GSK Agreement. OTL-300 has received orphan drug designation from the EMA for the treatment of beta-thalassemia major and intermediate. In addition, the EMA has granted Priority Medicines (PRIME) designation to OTL-300.

Ongoing clinical trials (cryopreserved formulation)

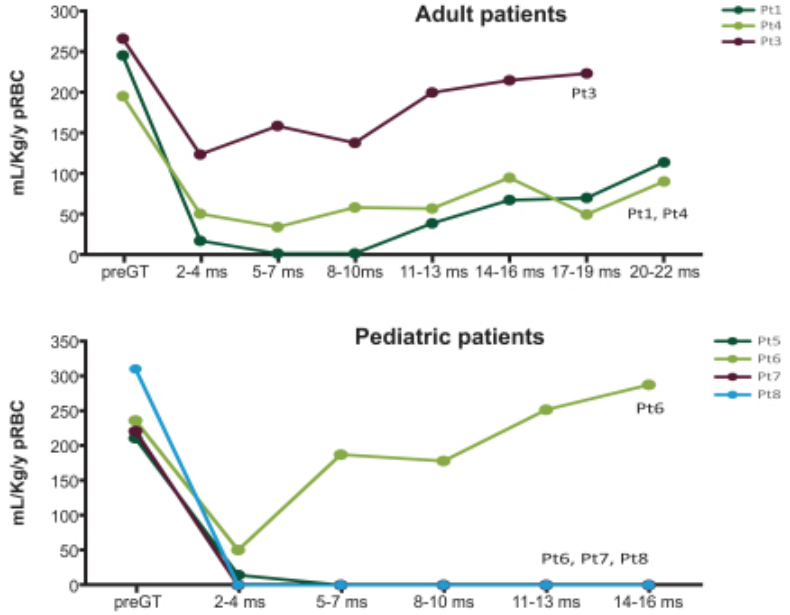
OTL-300 is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The target enrollment in this trial is nine patients with TDBT, and as of September 2018, all nine patients have received a single dose of a cryopreserved formulation of OTL-300. The patients evaluated in this trial include six pediatric patients aged three to 17 years, and three adult patients aged 18 years and over. Following conclusion of this trial at two-years post-treatment, patients will continue to be evaluated in a long-term follow-up clinical trial for an additional six year period.

The primary goals of these clinical trials are to assess the safety and efficacy of a cryopreserved formulation of OTL-300 in TDBT patients, as measured by, for example reduction in required blood transfusions to manage the patients' TDBT and overall survival at 24 months post-treatment.

Of the seven patients with at least 12 months of follow-up as of April 2018, significant reductions in transfusion frequency and volume requirements were observed in five patients, with three of the four pediatric patients being transfusion-free since approximately one month post-treatment. Following treatment, substantial reductions in transfusion volume requirements were observed in two out of three adult patients, with one patient transfusion-free over a period of nine months. The third adult patient at the most recent follow-up showed minimal reduction in transfusion frequency and volume requirements compared to the period before treatment with OTL-300.

The graphs below illustrate the reduction in required blood transfusions for up to 16 and 22 months post-treatment in pediatric and adult patients, respectively.

OTL-300 (TDBT): Blood transfusion requirements before and after treatment



As of April 2018, the date of the most recent safety report available to us, 100% overall survival has been observed, with a follow-up of up to approximately three years. Safety data from the nine patients treated in this clinical trial indicate OTL-300 was generally well-tolerated, with no instances of insertional mutagenesis up to approximately three years post-treatment. There were five SAEs reported, none of which were assessed by the investigator as being related to OTL-300. The SAEs included infection, neutropenia, gastroenteritis, and obstructive pancreatitis. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All SAEs resolved with standard of care treatment. Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR.

Preclinical data for our gene therapy programs

Each of our aforementioned lead programs has been evaluated in preclinical studies of murine models of the target indications. Preclinical development plans have been discussed with or reviewed by the FDA and EMA or E.U. Member State Authorities over the course of drug development interactions or approval of clinical trials.

Our preclinical gene therapy programs for the treatment of MPS-IIIA and MPS-IIIB

Disease overview

MPS-IIIA and MPS-IIIB are life-threatening metabolic diseases that cause accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within one to two years

after birth, MPS-IIIA and MPS-IIIB patients experience progressive neurological decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA and MPS-IIIB is between 10 to 25 years and 15 to 30 years, respectively.

The incidence of MPS-IIIA and MPS-IIIB are currently estimated to be one in 100,000 and one in 200,000 live births per year, respectively.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MPS-IIIA and MPS-IIIB. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MPS-IIIA and MPS-IIIB but does not slow or reverse the progression of the underlying disease. HSCT is not considered to be effective treatment options for these diseases. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MPS-IIIA and MPS-IIIB patients, their caregivers and families and healthcare systems.

Our Solution, OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB

We are developing OTL-201 and OTL-202 as autologous *ex vivo* gene therapies for treatment of patients with MPS-IIIA and MPS-IIIB, respectively. In both indications we believe preclinical studies in mice have shown that autologous *ex vivo* gene therapy has the potential to address the neurological manifestations of MPS-IIIA and MPS-IIIB. We plan to submit a CTA with the applicable regulatory authority in Europe for MPS-IIIA by the end of 2019 and plan to continue to progress preclinical development of MPS-IIIB.

We have obtained worldwide development and commercialization rights to OTL-201 for treatment of MPS-IIIA and OTL-202 for treatment of MPS-IIIB from The University of Manchester.

OTL-201 has received orphan drug designation from the EMA and FDA for the treatment of MPS-IIIA and has received rare pediatric disease designation from the FDA.

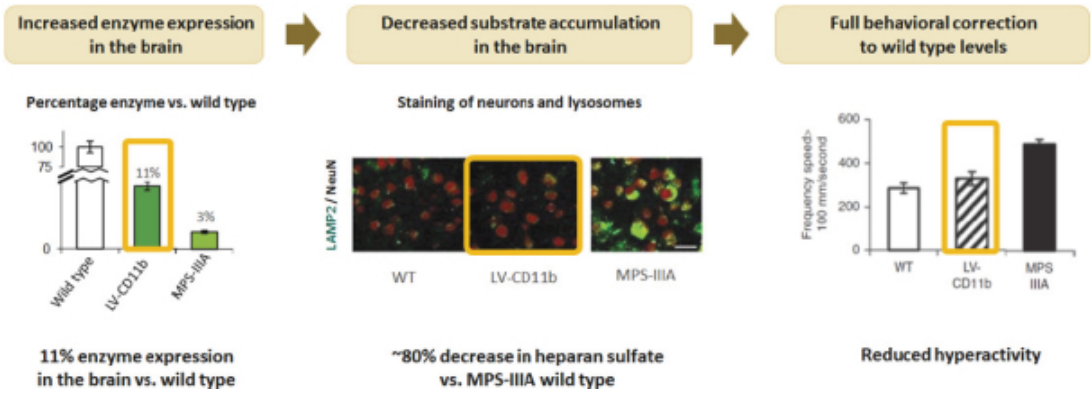
Preclinical studies

A comprehensive panel of preclinical studies has been performed by The University of Manchester, which we believe supports the use of OTL-201 in clinical trials.

In a mouse model of MPS-IIIA, engraftment of HSCs from a donor mouse modified with GFP using autologous *ex vivo* gene therapy with the selected vector for this program (a hCD11b-coSGSH lentiviral vector) was observed. Sustained gene expression of the GFP-modified HSCs was seen over a follow-up of approximately six months, which we believe supports the stability of the engraftment of modified cells.

Transplantation of gene-modified HSCs resulted in a 4.72-fold increase in enzyme activity relative to wild type enzyme levels and significantly elevated brain enzyme activity. Increased enzyme activity resulted in decreased heparan sulphate substrate accumulation in the brain and correction of behavioral abnormalities, such as hyperactivity and a reduced sense of danger, to normal levels.

The figures below illustrate the increased enzyme expression observed in the brain, the corresponding decreased substrate accumulation in the brain, and the resulting behavioural correction in a mouse model of MPS-IIIA.



Preclinical studies in a mouse model of MPS-IIIB have demonstrated correction of neurological activity, as measured by reduction in hyperactivity. Lentivirus vector optimization for OTL-202 for treatment of MPS-IIIB is ongoing.

Future applications of our autologous ex vivo gene therapy approach

We believe that our versatile autologous *ex vivo* gene therapy approach has the potential to deliver promising gene therapies to patients across a broad range of rare diseases. Although our initial focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from ADA-SCID, MLD, WAS, X-CGD and TDBT, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other rare diseases in our target franchise areas, including primary immune deficiencies, neurometabolic disorders and hemoglobinopathies, where *ex vivo* gene therapy has a comparably high probability of success. For example, we have option rights upon completion of clinical proof of concept studies for MPS-I, CGD and GLD, which would leverage the same autologous *ex vivo* gene therapy approach.

Our Regulatory Strategy

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment, and which are rare or ultra-rare indications, we believe our clinical programs may be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for the treatment of rare diseases, particularly life threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following one or more clinical trials in a limited patient population, following review of the trial's design, endpoints and clinical data by the applicable regulatory agencies. These determinations are based on the applicable regulatory agency's scientific judgement and these determinations may differ in the United States and the European Union.

For purposes of this prospectus, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial. In some cases applicable regulatory agency may require us to perform analytical studies or conduct additional clinical trials to support analytical comparability of drug product, for example by demonstrating comparability of drug product manufactured using HSCs derived from a patient's mobilized peripheral blood and drug product manufactured using HSCs derived from a patient's bone marrow and/or comparability of drug product that has been cryopreserved and fresh drug product. For purposes of this prospectus we refer to these clinical trials as supportive clinical trials. In addition, certain of our product candidates may be evaluated in clinical trials for which clinical data is not intended to be pooled with data from our registrational trials for purposes of a regulatory submission, but will be submitted to the applicable regulatory agencies for informational purposes. For purposes of this prospectus we refer to these trials as additional clinical trials. In addition, in some cases patients may be ineligible for participation in our clinical trials and may receive treatment under a compassionate use program. We expect that the available safety and efficacy results from all these trials would be included in any regulatory submission we may submit and the applicable regulatory agency with respect to each clinical program the applicable regulatory agency will make a determination as to whether the available data is sufficient to support a regulatory submission. See "Risk factors—The results from our clinical trials for OTL-101 for ADASCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates," "Risk factors—We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product," and "Risk factors—To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites."

Manufacturing

The diseases we are targeting affect patients across the world. Therefore, we are implementing our plans to build a commercial-scale manufacturing infrastructure and leverage technologies that will allow us to deliver our gene therapies globally.

Global supply network with experienced CMOs

We currently partner with a network of experienced CMOs, including Oxford BioMedica and MolMed S.p.A., for the supply of our vectors and/or drug product. We have established relationships with commercial CMO partners with the resources and capacity to meet our clinical and existing and expected initial commercial needs. Two of our vector CMOs currently manufacture for approved commercial gene therapy products. Our CMO partners also provide us with access to state-of-the art production technologies, as well as complementary geographic dispersity to mitigate supply chain risk.

Manufacturing efficiencies and scalability

We are in the process of implementing our plans to functionally close and/or automate some process steps for the manufacture of our gene therapies. We currently operate two development laboratory facilities in California and plan to invest in additional facilities to accommodate our expanding technical operations and implement in-house manufacture for some of our CGMP vector and drug product needs. We also continue to invest in the human talent and facility infrastructure required to support the initial development and validation of processes and controls for the manufacture of our product candidates. We believe this industrialization of our manufacturing processes will afford us more flexibility and control over our development programs. We are actively investing in improving the yield of vector and drug product production and enhancing transduction efficiency to lower cost of goods. We are also investigating automation of the entire drug production process. We believe these initiatives will allow us to increase production yield while lowering production costs for our programs.

Cryopreservation of our gene therapy programs

Cryopreservation of the gene-modified cells is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide. We have developed cryopreserved formulations of our OTL-101, OTL-102, OTL-200 and OTL-300 programs and are in the process of introducing a cryopreserved formulation of our OTL-103 program and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

In the cryopreservation process, a patient's gene-modified HSCs are frozen at extremely low temperatures and then stored to allow quality control testing and release to be performed before introducing the cells back into the patient. Our cryopreserved formulations are expected to have shelf-lives of months to years, enabling us to potentially distribute our products and product candidates from a few centralized manufacturing facilities to geographically dispersed treatment sites. Our ability to ultimately distribute our product candidates globally will facilitate access of the therapies to patients, and reduces the logistical burden on the patients and their families.

Intellectual property and barriers to entry

Our commercial success depends, in part, upon our ability to protect commercially important and proprietary aspects of our business, defend and enforce our intellectual property rights, preserve the confidentiality of our know-how and trade secrets, and operate without infringing misappropriating and otherwise violating valid and enforceable intellectual property rights of others. In particular, we strive to protect the proprietary aspects of our business and to develop barriers to entry that we believe are important to the development and commercialization of our gene therapies. For example, where appropriate, we develop, or acquire exclusive rights to, clinical data for Strimvelis and each of our product candidates, know-how and trade secrets associated with Strimvelis and each of our product candidates. However, we do not own any patents or patent applications that cover Strimvelis or any of our product candidates. We in-license from UCLB and UCLA one family of patent applications directed at OTL-101. We cannot guarantee that patents will issue from any of these patent applications or from any patent

applications we or our licensors may file in the future, nor can we guarantee that any patents that may issue in the future from such patent applications will be commercially useful in protecting Strimvelis or our product candidates. In addition, we plan to rely on regulatory protection based on orphan drug exclusivities, data exclusivities and market exclusivities. See "—Government regulation" for additional information.

We currently rely primarily on know-how and trade secret protection for aspects of our proprietary technologies that we or our licensors believe are not amenable to or appropriate for patent protection, including, for example, clinical data and production information for Strimvelis and each of our product candidates. However, know-how and trade secrets can be difficult to protect. Although we take steps to protect our know-how, trade secrets and other proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or similar know-how, trade secrets or proprietary information or may otherwise gain access to such know-how, trade secrets and other proprietary information or such know-how, trade secrets or other proprietary information may otherwise become known. Moreover, we cannot guarantee that our confidentiality agreements will provide meaningful protection or that they may not be breached and we may not have an adequate remedy for any such breach. As a result, we may be unable to meaningfully protect our know-how, trade secrets and other proprietary information.

In addition, with regard to patent protection, the scope of coverage being sought in a patent application may be reduced significantly before a patent is issued, and even after issuance the scope of coverage may be challenged. As a result, we cannot guarantee that any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

With regards to our OTL-101 product candidate, we have exclusive, worldwide, sub-licensable, licenses pursuant to the UCLB/UCLA Agreement to clinical data and to a patent family containing one pending U.S. patent application with composition of matter claims directed to the OTL-101 product candidate and its use in the treatment of ADA-SCID, and one pending counterpart European patent application. The U.S. patent application, if issued as a U.S. patent, would be expected to expire in 2036, without taking a potential patent term adjustment or extension into account. In addition, under the UCLB/UCLA Agreement, we have non-exclusive, worldwide, sub-licensable, licenses to know-how and materials relating to the OTL-101 product candidate.

With regards to Strimvelis, OTL-103, OTL-200 and OTL-300, and as discussed in detail in "—License agreements", we have exclusive, worldwide, sub-licensable licenses pursuant to the GSK Agreement and the R&D Agreement to anonymized patient-level data arising from the clinical trials of Strimvelis, OTL-103, OTL-200 and OTL-300 and know-how, including other clinical data and production information relating to Strimvelis, OTL-103, OTL-200, and OTL-300.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment, which provides additional term caused by administrative delays at the USPTO in

granting a patent, or may be shortened it a patent is terminally disclaimer over another patent with an earlier expiration date.

Furthermore, in the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Amendments as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. In the future, if we obtain an issued U.S. patent covering one of our present or future product candidates, and if such product candidate receives FDA approval, we expect to apply for a patent term extension, if available, to extend the term of the patent covering such approved product candidate. We also expect to seek patent term extensions in any jurisdictions where they are available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such an extension should be granted, and even if granted, the length of such an extension.

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, GSK novated to us their R&D Agreement with Telethon-OSR, which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Milan, Italy for MPS-I, CGD and GLD.

Under the GSK Agreement, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we are required to first use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. We are also required to use best endeavors to file a BLA for OTL-103 for WAS in the United States and to use commercially reasonable efforts to file an MAA for OTL-103 in Europe, and to subsequently market, sell and promote OTL-103 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and file an MAA or BLA, as applicable, for OTL-300 for TDBT in either the United States or Europe. In addition, we must also use best endeavors to maintain the MAA and regulatory designations for Strimvelis in the European Union and to continue to make Strimvelis available to eligible patients until an alternative gene therapy product has received marketing approval in Europe. We must also continue to make Strimvelis available at the San Raffaele Hospital for as long as a minimum number of patients are treated and entitled to receive reimbursement for the provision of Strimvelis, over a defined period. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement.

We are required to use commercially reasonable efforts to obtain a PRV from the FDA for each of Strimvelis, OTL-200, OTL-103 and OTL-300 and to transfer the first such PRV to GSK. GSK also has

an option to acquire at a defined price any PRVs granted to us thereafter for Strimvelis, OTL-200, OTL-103 and OTL-300. In the event that GSK does not exercise this option with respect to any PRV, we may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK.

GSK received a one-time upfront fee of £10.0 million under the GSK Agreement, and we issued to GSK 15,563,230 of our Series B-2 convertible preferred shares and have a payable due to GSK of £4.9 million.

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. We will pay a mid-single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048.

We may terminate our development and/or commercialization activities of any of the programs under the GSK Agreement, upon the occurrence of an SAE, or if we believe such program poses a safety risk to patients. GSK may require us to grant a third party a non-exclusive license under the intellectual property we have acquired from GSK under the GSK Agreement if we materially breach of our obligations to use best endeavors and/or commercially reasonable efforts to develop and commercialize the acquired programs and fail to develop and implement a mutually agreeable plan to cure such material breach within a specified time period. The foregoing license only continues until such time as we cure our material breach and we must pay GSK all amounts we receive from the third party in connection with such license.

Telethon-OSR research and development collaboration and license agreement

In April 2018, in connection with our entering into the GSK Agreement, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement with Telethon-OSR for the research, development and commercialization of *ex vivo* HSC gene therapies for ADA-SCID, WAS, MLD, TDBT, X-CGD, MPS-I, and GLD.

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, sublicensable, worldwide license under certain intellectual property rights to develop and commercialize certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD,

TDBT, X-CGD, MPS-I and GLD. At the time we entered into the deed of novation agreement, GSK had completed development, launched and commercialized Strimvelis for ADA-SCID in EU, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to the WAS, MLD and TDBT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID, WAS, MLD and TDBT collaboration programs pursuant to the GSK Agreement and to the deed of novation.

Under the R&D Agreement, Telethon-OSR is required to use commercially reasonable efforts to conduct each of the collaboration programs in accordance with development plans approved by a joint steering committee. With respect to those programs in relation to which our option has been exercised, we are required to use commercially reasonable efforts to develop, obtain regulatory approval, launch and promote in both the European Union and the United States all licensed products and to commercialize and manufacture such products at levels sufficient to meet commercial demands. We are required to use best efforts to renew the EU marketing authorization for Strimvelis to enable patients to be treated at the San Raffaele hospital from all referring centers globally, as permitted by applicable law. With certain exceptions, Telethon-OSR is responsible for all costs and activities associated with the collaboration programs prior to our exercise of the option for any such program. We are responsible for the costs and activities associated with the continued development of Strimvelis and each program for which an option under the R&D Agreement is exercised.

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are also required to pay Telethon-OSR a fee in connection with the exercise of our option for each collaboration program. We are obligated to pay up to an aggregate of €31M in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDBT programs) and we may become obligated to pay up to an aggregate of €70.5M in connection with option fees and product development milestones with respect to those programs for which we have not to date exercised our exclusive license option under this agreement (that is, for X-CGD, MPS-I and GLD programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

Unless terminated earlier, the R&D Agreement will expire (i) on a product-by-product and country-by-country basis upon the expiration of all payment obligations with respect to such product in such country, (ii) in its entirety upon the expiration of all payment obligations with respect to the last product in all countries in the world and (iii), on a program-by-program basis when no vector or gene therapy product is being researched, developed or commercialized. Either we or Telethon-OSR may terminate the R&D Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time. Additionally, either we or Telethon-OSR may terminate

involvement in a collaboration program for compelling safety reasons, and either we or Telethon-OSR may terminate the R&D Agreement if the other party becomes insolvent. We may also terminate the R&D Agreement either in its entirety or on a program-by-program basis for any reason upon notice to Telethon-OSR.

UCLB/UCLA License Agreement

In February 2016, we entered into a license agreement, or the UCLB/UCLA Agreement, with UCLB and UCLA, pursuant to which we obtained an exclusive, worldwide, sublicenseable license to certain technology, clinical data, manufacturing know-how, and intellectual property rights related to the production of virally transduced HSCs for treatment of patients with ADA-SCID, in addition to certain other rare disease indications. We must use diligent efforts to develop and commercialize a gene therapy product in each of the foregoing indications in the United States, United Kingdom and at least one of France, Germany, Italy and Spain as soon as reasonably possible.

UCLB received an aggregate upfront fee of £1,400,000 and a patent reimbursement fee of £12,524.10 under the UCLB/UCLA Agreement, and we issued to UCLB 4,300,000 and 1,529,545 of our ordinary shares in 2016 and 2017, respectively, and not reflecting the 1-for-0.8003 reverse share split. We are also required to make certain annual administration payments to UCLB upon our receipt of VAT invoices.

Under the UCLB/UCLA Agreement, we are also obligated to pay UCL royalties ranging from low to mid-single-digit percentages on net sales of each of the product candidates subject to the UCLB/UCLA Agreement that receive marketing approval. Our royalty obligations under the UCLB/UCLA Agreement terminate in February 2041. In addition, we are required to pay to UCLB milestone payments up to an aggregate of £28.85 million upon achievement of our first, second and third marketing approvals of product candidates under the UCLB/UCLA Agreement.

Unless terminated earlier, the UCLB/UCLA Agreement will expire in February 2041. We may terminate the UCLB/UCLA Agreement in its entirety or with respect to either UCLB or UCLA for any reason upon prior written notice. Additionally, either we or UCLB may terminate the UCLB/UCLA Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time, or if the other party becomes insolvent.

Oxford BioMedica License and Development Agreement

In November 2016, we entered into a license and development agreement, or the Oxford Development Agreement, with Oxford BioMedica (UK) Limited, or Oxford BioMedica, for the development of gene therapies for ADA-SCID, MPS-IIIA and certain other diseases that we may request be included under the Oxford Development Agreement, such other diseases referred to as Subsequent Indications. The Oxford Development Agreement was amended in June 2017, May 2018, July 2018 and September 2018.

Pursuant to the Oxford Development Agreement, Oxford BioMedica granted us an exclusive, worldwide license under certain intellectual property rights for the purposes of research, development and commercialization of *ex vivo* gene therapy products for the treatment of ADA-SCID, MPS-IIIA and Subsequent Indications, except that such license is non-exclusive to the extent the treatment of a Subsequent Indication is the subject of a certain previous license granted by Oxford BioMedica. Oxford BioMedica also granted us a non-exclusive, worldwide license under

certain intellectual property rights for the purposes of research, development, commercialization and manufacture of *ex vivo* gene therapy products for the treatment of certain diseases other than ADA-SCID, MPS-IIIA and Subsequent Indications. Under the Oxford Development Agreement, Oxford BioMedica is required to use commercially reasonable efforts to perform the activities set forth in a collaboration plan approved by a joint steering committee, and we are responsible for certain costs of the activities set forth in such collaboration plan.

As consideration for the licenses granted under the agreement, we issued 735,000 of our ordinary shares to Oxford BioMedica, not reflecting the 1-for-0.8003 reverse share split. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 188,462 ordinary shares upon the achievement of the first milestone in November 2017 and 188,462 ordinary shares were issued upon the achievement of further milestones in August 2018, in each instance, not reflecting the 1-for-0.8003 reverse share split. We will be required to issue additional ordinary shares to Oxford BioMedica upon achievement of the remaining milestone under the Oxford Development Agreement. Additionally, we are obligated to pay low single-digit royalties on net sales of licensed products until January 31, 2039. The foregoing royalties are reduced by a mid-double digit percentage in the case of compassionate use of a licensed product in a country until the first commercial sale following marketing authorization in such country. We are also required to pay a set monthly fee to Oxford BioMedica in the event we use a certain Oxford BioMedica system for generating stable cell lines.

Unless terminated earlier, the Oxford Development Agreement will expire when no further payments are due to Oxford BioMedica. We may terminate the performance of the collaboration plan upon notice to Oxford BioMedica, and either party may terminate the performance of the collaboration plan or the Oxford Development Agreement if the other party commits a material breach that is not cured within a certain period of time. Either party may also terminate the Oxford Development Agreement in the event the other party becomes insolvent.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. While we believe that our portfolio of product candidates and scientific expertise in gene therapy provides us with competitive advantages, we face potential competition from many different sources.

We face competition not only from gene therapy companies, but also from companies that are developing novel, non-gene therapy approaches or improving existing treatment approaches. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, if approved.

We are currently aware of the following competitive approaches:

- **ADA-SCID**: The current standards of care for the treatment of ADA-SCID are HSCT and chronic ERT. Adagen, marketed by Leadiant Biosciences, is the only approved ERT for ADA-SCID. We are aware that Leadiant Biosciences has filed a supplemental BLA for elapegademase, a pegylated recombinant version of Adagen, for the treatment of ADA-SCID.
- **MLD**: There is currently no effective treatment option for patients with MLD. HSCT has demonstrated limited efficacy in arresting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. We are aware that the Institut National de la Santé Et de la Recherche Médicale and Bicêtre hospital in Paris are investigating intracerebral gene therapy for MLD using an

adenovirus AAV-10 vector in a clinical trial. We are also aware that Shire is investigating ERT for MLD with a biweekly intrathecal infusion. We are also aware that Shenzhen University is evaluating a lentiviral *ex vivo* gene therapy for MLD.

- **WAS**: The current standard of care for WAS is HSCT. Patients who are unable to match with a blood donor or who are otherwise ineligible for HSCT may pursue palliative care options, including intravenous immunoglobulin and antimicrobials to prevent and treat infections, topical corticosteroids to manage outbreaks of eczema, platelet transfusions to treat severe bleeds, and immunosuppressive drugs, such as rituximab, to counter autoimmune manifestations. Splenectomy may also be used to treat thrombocytopenia. These palliative approaches do not slow disease progression or address the underlying etiology of WAS. We are also aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with autologous *ex vivo* lentiviral gene therapy. We do not currently have a license or an option to acquire a license from Généthon to these clinical trials in WAS and accordingly Généthon or its licensee may elect to compete against us with respect to this program. To our knowledge no other gene therapy approaches are being currently investigated in WAS.
- **X-CGD**: Management options for patients with X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are aware that Généthon is sponsoring a clinical trial for X-CGD with an autologous *ex vivo* lentiviral gene therapy in France. We are party to an exclusive option and license agreement with Généthon, pursuant to which we have the right to exercise an option with respect to this ongoing clinical trial, which option expires in June 2019. In the event we elect not to exercise this option, Généthon or its licensee may elect to pursue a competitive program in X-CGD using any intellectual property or clinical data derived from this ongoing clinical trial.
- **TDBT:** The current standard of care for the treatment of TDBT involves chronic blood transfusions to address anemia combined with iron chelation therapy to manage the iron overload often associated with such chronic blood transfusions. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. TDBT is a highly competitive research area with several novel approaches under investigation. We are aware that bluebird bio is investigating LentiGlobin, an autologous *ex vivo* gene therapy, for treatment of TDBT and sickle cell disease. In October 2018, bluebird bio announced that the EMA had accepted its MAA for Lentiglobin for the treatment of adolescents and adults with TDBT and a non-ß0/ß0 genotype. bluebird bio has publicly announced its intention to file a BLA in the United States for Lentiglobin in the future. In addition, Memorial Sloane Kettering Cancer Center has been conducting a clinical trial utilizing a lentiviral vector. In addition, we are aware that Sangamo is investigating zinc finger nuclease-mediated gene-correction techniques in TDBT. Several other groups are developing gene editing approaches for beta-thalassemia, including CRISPR Therapeutics, EDITAS and Intellia Therapeutics. CRISPR Therapeutics' CTA for its gene editing approach for beta-thalassemia was approved in 2018. Several other non-gene therapy approaches are under investigation to improve treatment outcomes in beta-thalassemia.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being

concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the research, development, clinical trial, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Each clinical trial protocol for a gene therapy product must be reviewed by the FDA, and, in some instances, the NIH, through its RAC. FDA approval must be obtained before the marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the CBER regulates gene therapy products. The CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in IND for gene therapies. In July 2018, FDA issued draft guidance documents for public comment involving various aspects of gene therapy product development, review, and approval. If finalized by FDA, these guidance documents would represent FDA’s current thinking on the development of gene therapy products for specific disease categories, including for rare diseases, as well as update and replace FDA’s previous guidance on manufacturing issues related to gene therapy products and long-term follow-up observational studies for gene therapy products.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional laws and regulations restricting or prohibiting the processes we may use. Federal and state legislatures, agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive laws and regulations or interpretations of existing laws or regulations, or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological products development process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an independent IRB or ethics committee at each clinical trial site before each study may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as GCPs and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with CGMP to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or CGTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product biological characteristics, chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation are submitted to and the study is registered with the NIH Office of Science Policy, or OSP, pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA; however, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations, at one of its quarterly public meetings. The OSP will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy

protocol. RAC proceedings and reports are posted to the OSP web site and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. An IND is a request for authorization from the FDA to ship an unapproved, investigational product in interstate commerce and to administer it to humans, and must become effective before clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical trials due to, among other considerations, unreasonable or significant safety concerns, inability to assess safety concerns, lack of qualified investigators, a misleading or materially incomplete investigator brochure, study design deficiencies, interference with the conduct or completion of an a study designed to be adequate and well-controlled for the same or another investigational drug, insufficient quantities of investigational product, lack of effectiveness, or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues or circumstances will not arise that delay, suspend or terminate such studies.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor’s control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA’s regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial and its related documentation must be reviewed and approved by an IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Clinical research involving recombinant DNA that is subject to NIH guidelines also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

In August 2018, the NIH published a notice in the Federal Register to seek public comment on its proposal to amend the NIH Guidelines to streamline oversight for human gene transfer clinical

research protocols and reduce duplicative reporting requirements while focusing the NIH Guidelines more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The notice included proposed amendments to eliminate RAC review and reporting requirements to NIH for human gene transfer research protocols and to modify the roles and responsibilities of investigators, institutions, IBCs, the RAC, and the NIH to be consistent with these goals.

Clinical trials typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2*. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *Phase 3*. Clinical trials are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for treatment of rare diseases, particularly life threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following a single clinical trial in a limited patient population, sometimes referred to as a Phase 1/2 trial, but which may be deemed a pivotal or registrational trial following review of the trial's design and primary endpoints by the applicable regulatory agencies. Determination of the requirements to be deemed a pivotal or registrational trial is subject to the applicable regulatory authority's scientific judgement and these requirements may differ in the U.S. and the European Union.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical

trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with CGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

After the completion of clinical trials of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the FDA accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. In most cases, the submission of a BLA is subject to a substantial application user fee, although the fee may be waived under certain circumstances. Under the performance goals and policies implemented by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA targets ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates,

and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a ‘‘filing’’ decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with CGMP to assure and preserve the product’s identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult or novel questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a REM is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. To assure CGMP, CGTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a novel product (e.g., new active ingredient, new indication, etc.) must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data

obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the FDA decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, including to subpopulations of patients, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings precautions or interactions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the FDA's breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, the FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Under priority review, the FDA's goal is to review an application in six months once it is filed, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

RMAT designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of RMAT, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. RMAT do not include

those HCT/Ps regulated solely under section 361 of the PHS Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like some of FDA's other expedited development programs, RMAT designation does not change the standards for approval but may help expedite the development or approval process.

Post-approval requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to CGMP. We currently rely, and may continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the CGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of CGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to

comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with CGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain CGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four and 12 year exclusivity periods from the time of first licensure of the product. FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. “First licensure” typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the “first licensure” of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Additional regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Government regulation outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products as well as authorization and approval of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical trial may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Regulation in the European Union

In the European Union, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the European Union and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to regenerate, repair or replace a human tissue. We anticipate that our gene therapy development products would be regulated as ATMPs in the European Union.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit an MAA. The application used to submit the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar

application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five (5) in ten thousand (10,000) persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Pediatric development

In the European Union, companies developing a new medicinal product must agree upon a Pediatric Investigation Plan, or PIP, with the EMA, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-approval controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Other healthcare laws and compliance requirements

In addition to FDA restrictions on the marketing of pharmaceutical products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our business or financial arrangements and relationships through which we market, sell and distribute the gene therapies for which we obtain approval. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback,

bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;

- the federal civil and criminal false claims laws and civil monetary penalties laws, such as the federal False Claims Act, which impose criminal and civil penalties and authorize civil whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement or record material to a false or fraudulent claim or from knowingly or making a false statement to avoid, decrease, or conceal an obligation to pay or transmit money or property to the federal government;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary's selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payer (e.g., public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious, or fraudulent statements or representations in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters; similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;
- the federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, which requires applicable manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program to report annually to the U.S. Department of Health and Human Services, CMS, information related to payments or other transfers of value made to physicians (defined to include doctors, dentists, optometrists, podiatrists and

chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

Additionally, we are subject to state and foreign equivalents of each of the healthcare laws and regulations described above, among others, some of which may be broader in scope and may apply regardless of the payer. Many U.S. states have adopted laws similar to the federal Anti-Kickback Statute and False Claims Act, and may apply to our business practices, including, but not limited to, research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental payors, including private insurers. In addition, some states have passed laws that require pharmaceutical companies to comply with the April 2003 Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers and/or the Pharmaceutical Research and Manufacturers of America's Code on Interactions with Healthcare Professionals. Several states also impose other marketing restrictions or require pharmaceutical companies to make marketing or price disclosures to the state. There are ambiguities as to what is required to comply with these state requirements and if we fail to comply with an applicable state law requirement, we could be subject to penalties. Finally, there are state and foreign laws governing the privacy and security of health information, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines, imprisonment and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states.

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, any of which could adversely affect our ability to operate our business and our financial results. In addition, our gene therapy program, Strimvelis, was approved by the EMA in 2016, and the

approval and commercialization of Strimvelis subjects us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. The approval and commercialization of any of our other gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

The risk of our being found in violation of these laws is increased by the fact that many of these laws have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain a robust system to comply with multiple jurisdictions with different compliance and reporting requirements increases the possibility that a healthcare company may violate one or more of the requirements. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial cost.

Healthcare reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to new annual, nondeductible fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; expanded healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance; expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; expanded the entities eligible for discounts under the PHS Act's pharmaceutical pricing program, also known as the 340B Drug Pricing Program; created new requirements to report financial arrangements with physicians and teaching hospitals, commonly referred to as the Physician Payments Sunshine Act; created a new requirement to annually report the identity and quantity of drug samples that manufacturers and authorized distributors of record provide to physicians; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established the Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been numerous judicial and Congressional challenges to certain aspects of the ACA. In January 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on, in part, states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 12, 2017, President Trump signed the Executive Order Promoting Healthcare Choice and Competition, and soon after announced the termination of the cost-sharing subsidies that reimburse insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has recently proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

The TCJA includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the “individual mandate.” Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called “Cadillac” tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device exercise tax on non-exempt medical devices. Further, the BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.” Congress will likely consider other legislation to replace or modify elements of the ACA. We continue to evaluate the effect that the ACA and its possible repeal, replacement or further modification could have on our business. It is uncertain the extent to which any such changes may impact our business or financial condition.

In addition, the Budget Control Act of 2011 and the Bipartisan Budget Act of 2015 led to aggregate reductions of Medicare payments to providers of up to 2% per fiscal year that will remain in effect through 2027 unless additional Congressional action is taken. Further, on January 2, 2013, the American Taxpayer Relief Act was signed into law, which, among other things, reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which have resulted in several recent Congressional inquiries and proposed bills designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

We expect that additional foreign, federal and state healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in limited coverage and reimbursement and reduced demand for our products, once approved, or additional pricing pressures.

Coverage and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from payors. Payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payer will pay for the product. Payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Moreover, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, coverage and reimbursement for products can differ significantly from payer to payer. One payor's decision to cover a particular medical product or service does not ensure that other payers will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate.

As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payer separately and will be a time-consuming process.

Payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain and maintain coverage and reimbursement for any product, we may need to conduct expensive clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees

As of June 30, 2018, we had 100 full-time employees, 13 of whom have Ph.D. or M.D. degrees. Of these full-time employees, 70 employees are engaged in research and development activities and 30 employees are engaged in finance, legal, human resources, facilities and general management. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relationship with our employees to be good.

Facilities

Our principal office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom. We lease approximately 9,626 square feet of office space at this location and our lease for this location extends through January 2023. We also lease approximately 5,981 square feet of office space in Boston, Massachusetts, 14,138 square feet of research and development laboratories and office space in Menlo Park, California, and 4,472 square feet of research and development laboratories and office space in Foster City, California. We believe that suitable additional or substitute space will be available as needed to accommodate any future expansion of our operations.

Legal proceedings

From time to time, we may be a party to litigation or subject to claims incident to the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we currently believe that the final outcome of these ordinary course matters will not have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. We are not currently a party to any material legal proceedings.

Management

Executive officers and directors

The following table sets forth the name, age and position our executive officers and directors as of September 30, 2018.

Name	Age	Position(s)
Executive Officers:		
Mark Rothera	56	President, Chief Executive Officer and Director
Frank E. Thomas	48	Chief Financial Officer and Chief Business Officer
Bobby Gaspar, M.D., Ph.D.	54	Chief Scientific Officer and Director
Non-Executive Directors:		
James A. Geraghty	63	Chairman of the Board of Directors
Joanne T. Beck, Ph.D.	57	Director
Marc Dunoyer	65	Director
Jon Ellis, Ph.D.	51	Director
Alex Pasteur, Ph.D.(1)	47	Director
Charles A. Rowland, Jr.	60	Director
Hong Fang Song	53	Director
Elise Wang(2)	59	Director

(1) Dr. Pasteur has indicated to us his intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

(2) Ms. Wang has indicated to us her intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Executive officers

Mark Rothera has served as our President, Chief Executive Officer and a member of our board of directors since August 2017. Previously, from April 2013 to August 2017, Mr. Rothera served as the Chief Commercial Officer of PTC Therapeutics, Inc., a public biopharmaceutical company. Prior to joining PTC Therapeutics, Inc., Mr. Rothera served as Global President of Aegerion Pharmaceuticals, Inc., a biopharmaceutical company, from April 2012 to January 2013. From January 2006 to March 2012, he served as Vice President and General Manager for the commercial operations of Shire Human Genetic Therapies, Inc. in Europe, the Middle East & Africa. Prior to joining Shire, Mr. Rothera served as Area VP Europe, Middle East and Africa for Chiron BioPharmaceuticals from September 2000 to April 2005. Prior to Chiron, Mr. Rothera held various global strategic and operational marketing and sales roles with French and UK operations of Glaxo Wellcome. Mr. Rothera holds an M.A. in Natural Science from Cambridge University, an M.B.A. from the European Institute for Business Administration and a Diploma in Company Direction from Institute of Directors, United Kingdom. We believe Mr. Rothera is qualified to serve on our board because of his executive experience in our industry.

Frank E. Thomas has served as our Chief Financial Officer and Chief Business Officer since January 2018. Previously, Mr. Thomas served as President and Chief Operating Officer of AMAG Pharmaceuticals, Inc., a publicly traded, specialty pharmaceutical company, from April 2015 to April 2017, as AMAG's Executive Vice President and Chief Operating Officer from May 2012 through April 2015 and as Executive Vice President, Chief Financial Officer and Treasurer from August 2011 through May 2012. Prior to AMAG, he served as Senior Vice President, Chief Operating Officer and Chief Financial Officer for Molecular Biometrics, Inc., a commercial stage

medical diagnostics company, from October 2008 to July 2011. Prior to Molecular Biometrics, Mr. Thomas spent four years at Critical Therapeutics, Inc., a public biopharmaceutical company, from April 2004 to March 2008, where he was promoted to President in June 2006 and Chief Executive Officer in December 2006 from the position of Senior Vice President and Chief Financial Officer. He also served on the Board of Directors of Critical Therapeutics from 2006 to 2008. Prior to 2004, Mr. Thomas served as the Chief Financial Officer and Vice President of Finance and Investor Relations at Esperion Therapeutics, Inc., a public biopharmaceutical company. Since June 2014, Mr. Thomas has served on the board of directors of Zafgen, Inc., a publicly traded biopharmaceutical company. Since July 2017, Mr. Thomas has served on the Board of Directors of Spero Therapeutics, Inc., a publicly traded, development-stage biotechnology company. Mr. Thomas was a member of the Board of Directors of the Massachusetts Biotechnology Council from 2007 to 2015. Mr. Thomas holds a B.B.A. from the University of Michigan, Ann Arbor.

Bobby Gaspar, M.D., Ph.D. has served as our Chief Scientific Officer and as a member of our board of directors since February 2016. Dr. Gaspar joined UCL and GOSH with an interest in gene therapy. Since October 2007, he has been professor of pediatrics and immunology at the UCL Institute of Child Health and Honorary Consultant in pediatric immunology at GOSH. Dr. Gaspar holds an M.B. B.S. from Kings College London and a Ph.D. from UCL. We believe Dr. Gaspar is qualified to serve on our board of directors because of his scientific and industry experience in the field in which we operate.

Non-executive directors

James A. Geraghty has been chairman of our board of directors since May 2018. He also serves as chairman of the boards of directors of publicly traded biopharmaceutical companies Idera Pharmaceuticals, Inc., Juniper Pharmaceuticals, Inc., and Pieris Pharmaceuticals, Inc., and as a member of the board of directors of publicly traded AAV gene therapy company Voyager Therapeutics, Inc. and privately held biotechnology company Fulcrum Therapeutics, Inc. He served as an Entrepreneur in Residence at Third Rock Ventures, a venture capital firm, from May 2013 to October 2016. Prior to that, Mr. Geraghty served as Senior Vice President, North America Strategy and Business Development at Sanofi S.A., a publicly traded pharmaceutical company, from February 2011 to October 2013. Earlier, he held many roles at Genzyme Corporation from 1992 to 2011, most recently as Senior Vice President of International Development and an executive officer. While at Genzyme, his roles included President of Genzyme Europe and General Manager of Genzyme's cardiovascular business. He also served as Chairman, President and CEO of GTC Biotherapeutics, Inc. (formerly Genzyme Transgenics), a pharmaceutical company. Mr. Geraghty holds a B.A. in Psychology and English from Georgetown University, an M.S. in Clinical Psychology from the University of Pennsylvania, and a J.D. from Yale Law School. We believe Mr. Geraghty's experience as a senior executive and service on the boards of other life sciences companies qualifies him to serve on our board of directors.

Joanne T. Beck, Ph.D. has been a member of our board of directors since July 2018. Since April 2016, Dr. Beck has served as the Executive Vice President, Pharmaceutical Development & Operations at Celgene. Prior to joining Celgene, Dr. Beck was the Senior Vice President, Pharmaceutical Development at Shire from January 2012 to April 2016. From May 2004 to January 2012, Dr. Beck held leadership roles in both Pharmaceutical and Vascular Operations at Abbott, most recently as Head of Global Business Excellence and Strategic Program Management. Earlier in her career she had technical leadership roles at Amgen and Genentech. Dr. Beck holds a B.A. in Chemistry from Lewis and Clark College and a Ph.D. in Biochemistry and Molecular

Biology from Oregon Health and Science University. We believe Dr. Beck is qualified to serve on our board because of her executive experience in our industry.

Marc Dunoyer has been a member of our board of directors since May 2018. Since November 2013, Mr. Dunoyer has served as the chief financial officer at AstraZeneca plc, a publicly traded pharmaceutical company. At AstraZeneca, Mr. Dunoyer also held the role of Executive Vice President, Global Portfolio & Product Strategy from June 2013 to October 2013. Additionally, Mr. Dunoyer serves on the board of directors of AstraZeneca. Prior to joining AstraZeneca, from February 2010 to March 2013, Mr. Dunoyer served as the foundational Global Head of the Rare Diseases Unit at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Mr. Dunoyer also served on the company's corporate executive team and previously held the position of President for Asia-Pacific and Japan. Mr. Dunoyer has previously held international positions in operations and general management at Hoechst Marion Roussel, a wholly owned subsidiary of Sanofi S.A., a publicly traded pharmaceutical company, and holds an M.B.A. degree from the Hautes Etudes Commerciales and a Bachelor of Law degree from Paris University. We believe Mr. Dunoyer is qualified to serve on our board because of his executive experience in our industry.

Jon Ellis, Ph.D. has been a member of our board of directors since July 2018. Since January 2016, Dr. Ellis has served as the Vice President and Head, Science & Technology Licensing Pharmaceuticals R&D at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Dr. Ellis has also held the roles of Vice President & Head of Platforms BD & Academic, Vice President & Head of Platforms BD, Vice President & Head of Biopharmaceuticals BD, as well as the Head of Antibody Engineering and Biopharm Licensing. Prior to joining GSK in 2001, Dr. Ellis worked as a group leader at GlaxoWellcome plc, a former publicly traded pharmaceutical company, from November 1995 to January 2001. Prior to joining GlaxoWellcome in 1995, Dr. Ellis was a Senior Molecular Biologist at Wellcome Foundation Ltd, a former publicly traded pharmaceutical company, from November 1993 to November 1995. Prior to joining Wellcome Foundation in 1993, Dr. Ellis was a staff scientist at Quantum Biosystems Ltd from October 1992 to November 1993. Dr. Ellis holds a B.A. and M.A. from Magdalene College, University of Cambridge, a Ph.D. from the University of Cambridge, and an M.B.A. from Henley Management College. We believe Dr. Ellis is qualified to serve on our board because of his extensive experience in our industry.

Alex Pasteur, Ph.D. has been a member of our board of directors since November 2015. Dr. Pasteur is a London-based partner at F-Prime Capital Partners and has been a partner since January 2015. At F-Prime Capital Partners, Dr. Pasteur also held the role of Principal from October 2012 to December 2014. Additionally, Dr. Pasteur served as our Chief Executive Officer from September 2016 to September 2017. Previously, Dr. Pasteur worked at MVM Life Science Partners LLP in the USA and Europe. Dr. Pasteur holds an M.A. in Natural Sciences and a Ph.D. in Chemistry from Cambridge University. We believe Dr. Pasteur is qualified to serve on our board of directors because of his extensive experience in our industry. Dr. Pasteur has indicated to us his intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Charles A. Rowland, Jr. has been a member of our board of directors since July 2018. From April 2016 to February 2017, Mr. Rowland served as President and Chief Executive Officer of Aurinia Pharmaceuticals Inc., and as a member of the board of directors of Aurinia from July 2014 to February 2017. Mr. Rowland previously served as Vice President and Chief Financial Officer of ViroPharma Incorporated, an international biopharmaceutical company, from October 2008 until it was acquired by Shire plc, in January 2014. Mr. Rowland previously held positions of increasing responsibility at the following companies: Biovail Pharmaceuticals, Inc., Breakaway Technologies, Inc., Endo Pharmaceuticals Inc., Pharmacia Corporation, Novartis AG,

and Bristol-Myers Squibb Co. Mr. Rowland has served as a member of the board of directors, chairman of the compensation committee and member of the audit committee of Viking Therapeutics, Inc, since July 2017. Since January 2015, he has served as a member of the board of directors and chairman of the audit committee and compensation committee of Nabriva Therapeutics, AG, based in Dublin, Ireland. Since March 2015, Mr. Rowland has served as a member of the board of directors and chairman of the audit committee and compensation committee of Blueprint Medicines Corporation, a publicly traded biopharmaceutical company. Mr. Rowland served as a member of the board of directors and audit committee of Idenix Pharmaceuticals, Inc., a biopharmaceutical company, from June 2013, until it was acquired by Merck & Co., Inc. in August 2014. Mr. Rowland served as a member of the board of directors and chairman of the audit committee of Vitae Pharmaceuticals, Inc., from September 2014 until it was acquired by Allergan Inc., in September 2016. Mr. Rowland served as a member of the board of directors and chairman of the audit committee of BIND Therapeutics, Inc., from May 2014 to July 2016. Mr. Rowland holds a B.S. in Accounting from Saint Joseph's University and an M.B.A. with a finance concentration from Rutgers University. We believe that Mr. Rowland's extensive professional experience as a chief financial executive in the biotechnology and pharmaceutical industries and his experience serving as a director of various publicly traded biotechnology companies qualifies him to serve as a member of our board of directors.

Hong Fang Song has served as a member of our board of directors since September 2017. Ms. Song is the founder and has been a Senior Partner of ORI Capital since July 2015. Previously, from January 2010 to June 2015, Ms. Song was the Managing Director of the China Healthcare Business Division of Goldman Sachs, a multinational investment bank and financial services company. Ms. Song holds a B.A. in Economics from Fudan University, China and an M.A. in Economics from Claremont Graduate School in the United States. We believe Ms. Song is qualified to serve on our board because of her extensive experience in the healthcare sector.

Elise Wang has been a member of our board of directors since August 2018. Ms. Wang is currently a Principal on the Public Structured Finance group at Deerfield Management Company, L.P., and has been with Deerfield since 2010. Prior to joining Deerfield, from 2001 to 2007, Ms. Wang was a Senior Research Analyst and Managing Director in healthcare primarily covering the biotechnology industry at Citigroup. From 1996 to 2001, Ms. Wang was a Senior Research Analyst and Managing Director at PaineWebber Inc., where she covered biotechnology. Ms. Wang began her career in healthcare in 1987 as a venture capitalist and banker at PaineWebber Inc. and was an officer of PaineWebber Development Corporation, which managed entities invested in biotechnology and high technology companies. Ms. Wang holds an A.B. in Engineering Sciences with a specialty in Biomechanics from Harvard University and an M.B.A. from Harvard Business School. We believe Ms. Wang is qualified to serve on our board because of her executive experience in our industry. Ms. Wang has indicated to us her intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Family relationships

There are no family relationships among any of our executive officers or directors.

Corporate governance practices

We are a "foreign private issuer," as defined by the SEC. As a result, in accordance with Nasdaq listing requirements, we may rely on home country governance requirements and certain

exemptions thereunder rather than complying with Nasdaq corporate governance standards. While we voluntarily follow most Nasdaq corporate governance rules, we may choose to take advantage of the following limited exemptions:

- exemption from filing quarterly reports on Form 10-Q containing unaudited financial and other specified information or current reports on Form 8-K upon the occurrence of specified significant events;
- exemption from Section 16 rules requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades in a short period of time, which will provide less data in this regard than shareholders of U.S. companies that are subject to the Exchange Act;
- exemption from the Nasdaq requirement requiring disclosure of any waivers of the Code of Business Conduct and Ethics, or Code of Ethics, for directors and officers;
- exemption from the requirement to obtain shareholder approval for certain issuances of securities, including shareholder approval of share option plans;
- exemption from the requirement that our audit committee have review and oversight over all “related party transactions,” as defined in Item 7.B of Form 20-F;
- exemption from the requirement that our board have a compensation committee that is composed entirely of independent directors with a written charter addressing the committee’s purpose and responsibilities; and
- exemption from the requirement to have independent director oversight of director nominations.

We intend to follow U.K. corporate governance practices in lieu of Nasdaq corporate governance requirements as follows:

- We do not intend to follow Nasdaq Rule 5620(c) regarding quorum requirements applicable to meetings of shareholders. Such quorum requirements are not required under English law. In accordance with generally accepted business practice, our Articles of Association will provide alternative quorum requirements that are generally applicable to meetings of shareholders.
- We do not intend to follow Nasdaq Rule 5605(b)(2), which requires that independent directors regularly meet in executive sessions where only independent directors are present. Our independent directors may choose to meet in executive sessions at their discretion.

Although we may rely on certain home country corporate governance practices, we must comply with Nasdaq’s Notification of Noncompliance requirement (Nasdaq Rule 5625) and the Voting Rights requirement (Nasdaq Rule 5640). Further, we must have an audit committee that satisfies Nasdaq Rule 5605(c)(3), which addresses audit committee responsibilities and authority and requires that the audit committee consist of members who meet the independence requirements of Nasdaq Rule 5605(c)(2)(A)(ii).

Because we are a foreign private issuer, our directors and senior management are not subject to short-swing profit and insider trading reporting obligations under Section 16 of the Exchange Act. They will, however, be subject to the obligations to report changes in share ownership under Section 13 of the Exchange Act and related SEC rules.

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act, the rules adopted by the SEC and Nasdaq listing rules.

Accordingly, our shareholders will not have the same protections afforded to shareholders of companies that are subject to all of the corporate governance requirements of Nasdaq. For an overview of our corporate governance principles, see the section titled “Description of share capital and articles of association—Differences in corporate law.”

Composition of our board of directors

Our board of directors is currently composed of ten members. Dr. Pasteur and Ms. Wang, currently members of our board of directors, have each indicated to us their intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. Our board of directors has determined that, of our ten directors, no director other than Mark Rothera, our Chief Executive Officer, and Bobby Gaspar, our Chief Scientific Officer has a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of director and that each of these directors is “independent” as that term is defined under Nasdaq rules.

The Articles of Association provide that upon completion of this offering, our board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution. See “Description of share capital and articles of association—Post-IPO articles of association—Board of directors.”

In October 2018, we entered into a director nomination agreement with Glaxo Group Limited, or GSK, pursuant to which we have agreed to nominate and appoint to our board of directors a designee of GSK, initially Jon Ellis, during the period commencing upon the completion of this offering until such time as we obtain marketing approval and commercially launch OTL-200 for MLD. See “Related party transactions—Director nomination agreement.”

Committees of our board of directors

Our board of directors has three standing committees: an audit committee, a compensation committee and a nominating committee.

Audit committee

The audit committee consists of Charles A. Rowland, Jr., Marc Dunoyer and Jon Ellis, Ph.D., and assists the board of directors in overseeing our accounting and financial reporting processes. Mr. Rowland will serve as chairman of the audit committee. The audit committee consists

exclusively of members of our board who are financially literate, and Mr. Rowland is considered an “audit committee financial expert” as defined by applicable SEC rules and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations. Our board has determined that all of the members of the audit committee satisfy the “independence” requirements set forth in Rule 10A-3 under the Exchange Act. The audit committee will be governed by a charter that complies with Nasdaq rules.

The audit committee’s responsibilities will include:

- recommending the appointment of the independent auditor to the general meeting of shareholders;
- the appointment, compensation, retention and oversight of any accounting firm engaged for the purpose of preparing or issuing an audit report or performing other audit services;
- pre-approving the audit services and non-audit services to be provided by our independent auditor before the auditor is engaged to render such services;
- evaluating the independent auditor’s qualifications, performance and independence, and presenting its conclusions to the full board of directors on at least an annual basis;
- reviewing the adequacy of our internal controls with management and any remediation plan associated with any significant control deficiencies or material weaknesses;
- reviewing and discussing with management and our independent registered public accounting firm our financial statements and our financial reporting process; and
- reviewing, approving or ratifying any related party transactions.

Compensation committee

The compensation committee consists of Charles A. Rowland, Jr. and Joanne T. Beck, Ph.D. and Mr. Rowland will serve as chairman of the compensation committee. Under SEC and Nasdaq rules, there are heightened independence standards for members of the compensation committee, including a prohibition against the receipt of any compensation from us other than standard board member fees. Although foreign private issuers are not required to meet this heightened standard, all of our compensation committee members are expected to meet this heightened standard.

The compensation committee’s responsibilities will include:

- identifying, reviewing and proposing policies relevant to the compensation and benefits of our directors and executive officers;
- evaluating each executive officer’s performance in light of such policies and reporting to the board; and
- overseeing and administering our employee share option scheme or equity incentive plans in operation from time to time.

Nominating committee

The nominating committee consists of James Geraghty and Marc Dunoyer and Mr. Geraghty will serve as chairman of the nominating committee.

The nominating committee's responsibilities will include:

- drawing up selection criteria and appointment procedures for directors;
- recommending nominees for election to our board of directors and its corresponding committees;
- assessing the functioning of individual members of our board of directors and executive officers and reporting the results of such assessment to the board of directors; and
- developing corporate governance guidelines.

Code of business conduct and ethics

We have adopted a Code of Ethics, applicable to our and our subsidiaries' employees, independent contractors, senior management and directors, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the Code of Ethics is posted on our website, which is located at www.orchard-tx.com. Information contained on, or that can be accessed through, our website does not constitute a part of this prospectus and is not incorporated by reference herein.

Compensation of executive officers and directors

For the year ended December 31, 2016 and 2017, the aggregate compensation accrued or paid to the members of our board of directors and our executive officers for services in all capacities was $0.6 million and $5.1 million, respectively.

During and for the years ended December 31, 2016 and 2017, we had no performance based compensation programs or amount set aside or accrued by us to provide pension, retirement or similar benefits to members of our board of directors or executive officers.

Non-executive director compensation

The compensation of our non-executive directors is determined by our board as a whole, based on a review of current practices in other companies.

Equity incentive plans

2016 Employee share option plan with non-employee sub-plan and U.S. sub-plan

2016 Employee Share Option Plan

Our 2016 Plan was adopted by our board of directors on September 14, 2016 and approved by our shareholders on March 29, 2017 and became effective on September 14, 2016. Our 2016 Plan was subsequently amended by our board of directors on February 7, 2018 and May 25, 2018. The 2016 Plan allows for the grant of options to our employees and executive directors. The board of directors has determined not to grant any further awards under the 2016 Plan following completion of this offering.

The 2016 Plan is administered by our board of directors. The board of directors has the authority to take all actions and make all determinations under the 2016 Plan, to interpret the 2016 Plan

and award agreements and to adopt, amend and repeal rules for the administration of the 2016 Plan as it deems advisable, subject to certain limitations imposed under the 2016 Plan, and other applicable laws and stock exchange rules. The plan administrator also has the authority to determine which eligible service providers receive awards, grant awards, set the terms and conditions of all awards under the 2016 Plan, including any vesting and vesting acceleration provisions, subject to the conditions and limitations in the 2016 Plan.

The 2016 Plan provides for the grant of options to purchase our ordinary shares in the future upon written exercise notice. All awards under the 2016 Plan will be set forth in an option certificate, which will detail the terms and conditions of the awards, including any exercise conditions and lapse information.

In connection with certain corporate transactions, including a change of control, our board of directors has broad discretion to take action under the 2016 Plan to prevent the dilution or enlargement of intended benefits, or to facilitate the transaction or event. This includes providing for the assumption or substitution of awards by a successor entity. In addition, in the event of a change in control, the board of directors may accelerate the vesting and exercisability of any option in its discretion. The board of directors may also specify a period of up to 90 days following a change in control during which such options must be exercised and, if not so exercised, such options will terminate.

Our board of directors may amend or terminate the 2016 Plan at any time; however, no amendment, other than an amendment that increases the number of shares available under the 2016 Plan, may affect an award outstanding under the 2016 Plan without the consent of the affected participant.

Except as our board of directors may determine or provide in an option certificate, options granted under the 2016 Plan are generally non-transferrable, except by will or the laws of descent and distribution, and are generally exercisable only by the participant. With regard to tax withholding obligations arising in connection with awards under the 2016 Plan, and exercise price obligations arising in connection with the exercise of options under the 2016 Plan, the plan administrator may, in its discretion, accept cash, wire transfer or check, or a net exercise arrangement.

As of September 30, 2018, options to purchase 10,135,454 shares of common stock were outstanding under the 2016 Plan. Our board of directors has determined not to make any further awards under the 2016 Plan following the pricing of this offering.

2016 Non-Employee Sub-Plan

The 2016 Non-Employee Sub-Plan allows for the grant of options to our non-executive directors, consultants, advisers and other non-employee service providers. Except as modified, all provisions of the 2016 Plan are incorporated into the 2016 Non-Employee Sub-Plan and provides for awards to be made on identical terms to awards made under our 2016 Plan.

2016 U.S. Sub-Plan

The 2016 U.S. Sub-Plan allows for the grant of options to an employee, director or consultant who is a U.S. resident or U.S. taxpayer. The 2016 U.S. Sub-Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under

Section 422 of the Code, and options that do not so qualify. Except as modified, all provisions of the 2016 Plan are incorporated into the 2016 U.S. Sub-Plan and provides for awards to be made on identical terms to awards made under our 2016 Plan.

2018 Share Option and Incentive Plan

Our 2018 Plan was adopted by our board of directors in October 2018 and approved by our shareholders in October 2018 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The 2018 Plan will replace the 2016 Plan as our board of directors has determined not to make additional awards under the 2016 Plan following the closing of our initial public offering. The 2018 Plan allows the compensation committee to make equity-based and cash-based incentive awards to our officers, employees, directors and other key persons (including consultants). Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares.

We have initially reserved 4,254,741 ordinary shares, or the Initial Limit, for the issuance of awards under the 2018 Plan. The 2018 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 5% of the outstanding number of ordinary shares on the immediately preceding December 31, or such lesser number of shares as determined by our compensation committee, or the Annual Increase. This number is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

The shares we issue under the 2018 Plan will be authorized but unissued shares or shares that we reacquire. The ordinary shares underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by us prior to vesting, satisfied without any issuance of shares, expire or are otherwise terminated (other than by exercise) under the 2018 Plan and the 2016 Plan will be added back to the ordinary shares available for issuance under the 2018 Plan.

The maximum aggregate number of shares that may be issued in the form of incentive share options shall not exceed the Initial Limit cumulatively increased on January 1, 2019 and on each January 1 thereafter by the lesser of the Annual Increase for such year or 4,254,741 ordinary shares.

The 2018 Plan will be administered by our compensation committee. Our compensation committee has full power to select, from among the individuals eligible for awards, the individuals to whom awards will be granted, to make any combination of awards to participants, and to determine the specific terms and conditions of each award, subject to the provisions of the 2018 Plan. Persons eligible to participate in the 2018 Plan will be those full or part-time officers, employees, non-employee directors and other key persons (including consultants) as selected from time to time by our compensation committee in its discretion.

The 2018 Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under Section 422 of the Code, and options that do not so qualify. The option exercise price of each option will be determined by our compensation committee but may not be less than 100% of the fair market value of our ordinary shares on the date of grant. The term of each option will be fixed by our compensation committee and may not exceed 10 years from the date of grant. Our compensation committee will determine at what time or times each option may be exercised.

Our compensation committee may award share appreciation rights subject to such conditions and restrictions as it may determine. Share appreciation rights entitle the recipient to ordinary shares, or cash, equal to the value of the appreciation in our share price over the exercise price. The exercise price of each share appreciation right may not be less than 100% of the fair market value of the ordinary shares on the date of grant.

Our compensation committee may award restricted shares and restricted share units to participants subject to such conditions and restrictions as it may determine. These conditions and restrictions may include the achievement of certain performance goals and/or continued employment with us through a specified vesting period. Our compensation committee may also grant ordinary shares that are free from any restrictions under the 2018 Plan. Unrestricted shares may be granted to participants in recognition of past services or other valid consideration and may be issued in lieu of cash compensation due to such participant. Our compensation committee may grant cash bonuses under the 2018 Plan to participants, subject to the achievement of certain performance goals.

The 2018 Plan provides that in the case of, and subject to, the consummation of a “sale event” as defined in the 2018 Plan, all outstanding awards may be assumed, substituted or otherwise continued by the successor entity. To the extent that the successor entity does not assume, substitute or otherwise continue such awards, then (i) all share options and share appreciation rights will automatically become fully exercisable and the restrictions and conditions on all other awards with time-based conditions will automatically be deemed waived, and awards with conditions and restrictions relating to the attainment of performance goals may become vested and non-forfeitable in connection with a sale event in the compensation committee’s discretion and (ii) upon the effectiveness of the sale event, the 2018 Plan and all awards will automatically terminate. In the event of such termination, (i) individuals holding options and share appreciation rights will be permitted to exercise such options and share appreciation rights (to the extent exercisable) prior to the sale event; or (ii) we may make or provide for a cash payment to participants holding options and share appreciation rights equal to the difference between the per share cash consideration payable to shareholders in the sale event and the exercise price of the options or share appreciation rights (to the extent then exercisable).

Our board of directors may amend or discontinue the 2018 Plan and our compensation committee may amend the exercise price of options and amend or cancel outstanding awards for purposes of satisfying changes in law or any other lawful purpose but no such action may adversely affect rights under an award without the holder’s consent. Certain amendments to the 2018 Plan require the approval of our shareholders. No awards may be granted under the 2018 Plan after the date that is 10 years from the date of shareholder approval. No awards under the 2018 Plan have been made prior to the date of this prospectus.

2018 Employee Share Purchase Plan

Our 2018 Employee Share Purchase Plan, or the ESPP, was adopted by our board of directors in October 2018 and approved by our shareholders in October 2018 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The ESPP is intended to qualify as an “employee share purchase plan” within the meaning of Section 423(b) of the Code. Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares. The ESPP initially reserves and authorizes the issuance of up to a total of 850,948 ordinary shares to

participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 1,500,000 shares or (iii) such number of shares as determined by the ESPP administrator. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

All employees who have completed at least 30 days of employment and whose customary employment is for more than 20 hours per week are eligible to participate in the ESPP. However, any employee who owns 5% or more of the total combined voting power or value of all classes of shares is not eligible to purchase shares under the ESPP.

We will make one or more offerings each year to our employees to purchase shares under the ESPP. Unless otherwise determined by our compensation committee, offerings will usually begin on each January 1 and July 1 and will continue for six-month periods, referred to as offering periods. The first offering began on the effective date of the registration statement of which this prospectus is a part. Each eligible employee may elect to participate in any offering by submitting an enrollment form at least 15 business days before the relevant offering date.

Each employee who is a participant in the ESPP may purchase shares by authorizing payroll deductions of up to 15% of his or her base compensation during an offering period. Unless the participating employee has previously withdrawn from the offering, his or her accumulated payroll deductions will be used to purchase shares on the last business day of the offering period at a price equal to 85% of the fair market value of the shares on the first business day or the last business day of the offering period, whichever is lower. Under applicable U.S. tax rules, an employee's right to purchase shares under the ESPP may not accrue at a rate that exceeds $25,000 worth of ordinary shares, valued at the start of the purchase period, under the ESPP, for each calendar year in the purchase period.

The accumulated payroll deductions of any employee who is not a participant on the last day of an offering period will be refunded. An employee's rights under the ESPP terminate upon voluntary withdrawal from the plan or when the employee ceases employment with us for any reason.

The ESPP may be terminated or amended by our board of directors at any time. An amendment that increases the number of ordinary shares authorized under the ESPP and certain other amendments require the approval of our shareholders.

Employees

As of December 31, 2017, 2016 and 2015, we had 53, 16 and 0 employees, respectively. As of December 31, 2017, 32 of our employees was based outside of the United Kingdom. All of our employees were engaged in either administrative or research and development functions. None of our employees are covered by a collective bargaining agreement.

Insurance and indemnification

To the extent permitted by the Companies Act 2006, we are empowered to indemnify our directors against any liability they incur by reason of their directorship. We maintain directors'

and officers' insurance to insure such persons against certain liabilities. We expect to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering.

In addition to such indemnification, we provide our directors and executive officers with directors' and officers' liability insurance.

Insofar as indemnification of liabilities arising under the Securities Act may be permitted to our board of directors, executive officers, or persons controlling us pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Related party transactions

Since September 1, 2015, we have engaged in the following transactions with our directors, executive officers or holders of more than 5% of our outstanding share capital and their affiliates, which we refer to as our related parties. The share and per share numbers set forth below under this “Related party transaction” section have not been adjusted to reflect the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected prior to completion of this offering.

GSK asset purchase and license agreement

On April 11, 2018, we entered the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first approved gene therapy by the EMA, two late-stage clinical gene therapy programs in ongoing registrational studies: OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, under this agreement, GSK novated to us their R&D Agreement with the Telethon-OSR which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Italy for MPS-I, CGD and GLD.

Upon execution of the agreement, we paid GSK a one-time upfront fee of £10.0 million, and we issued GSK 15,563,230 of our Series B-2 convertible preferred shares. Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. We will pay a mid single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048. See “Business — License agreements — GSK asset purchase and license agreement” for further information regarding the GSK Agreement.

In connection with this agreement, we also entered into (i) a transitional services agreement with GSK on April 11, 2018, pursuant to which GSK has agreed to provide us certain transitional services in connection with the transfer of the assets acquired under the GSK Agreement, and (ii) an inventory sale agreement with GSK on April 11, 2018, pursuant to GSK agreed to transfer certain inventory related to the assets acquired under the GSK Agreement.

As a result of the GSK Agreement, GSK is currently a greater than 5% beneficial owner of our outstanding ordinary shares.

Director nomination agreement

In October 2018, we entered into a director nomination agreement with Glaxo Group Limited, or GSK, pursuant to which we have agreed to nominate and appoint to our board of directors a

designee of GSK during the period commencing upon the completion of this offering until such time as we obtain marketing approval and commercially launch OTL-200 for MLD.

Subscription of our Series A convertible preferred shares

In February 2016, with subsequent closings in May 2016, July 2016, August 2016, January 2017 and February 2017, we sold an aggregate of 21,000,000 shares of our Series A convertible preferred shares at a purchase price of £1.00 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series A convertible preferred shares by related persons:

Shareholder	Series A convertible preferred shares	Total purchase price
Affiliates of F-Prime Capital(1)	20,000,001	£ 20,000,001

(1) Consists of (i) 10,000,001 shares of Series A convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 10,000,000 shares of Series A convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital is a holder of 5% or more of our outstanding ordinary shares.

Subscription of our Series B convertible preferred shares

In March 2017, with subsequent closings in August 2017, October 2017, December 2017 and January 2018, we sold an aggregate of 21,198,154 shares of our Series B convertible preferred shares at a subscription price of £4.019 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series B convertible preferred shares by related persons:

Shareholder	Series B convertible preferred shares	Total purchase price
Entities affiliated with F-Prime Capital(1)	3,000,000	£ 12,057,000
Scottish Mortgage Investment Trust plc(2)	4,000,000	£ 16,076,000
Mark Rothera(3)	49,763	£ 199,998

(1) Consists of (i) 1,500,000 shares of Series B convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 1,500,000 shares of Series B convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital is a holder of 5% or more of our outstanding ordinary shares.

(2) Scottish Mortgage Investment Trust plc is a holder of 5% or more of our outstanding ordinary shares.

(3) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

Subscription of our Series C convertible preferred shares

In August 2018, we sold an aggregate of 17,421,600 shares of our Series C convertible preferred shares at a purchase price of $8.61 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series C convertible preferred shares by related persons:

Shareholder	Series C convertible preferred shares	Total purchase price
Entities affiliated with Deerfield Management Company(1)	5,807,200	$ 49,999,992
Scottish Mortgage Investment Trust plc(2)	871,080	$ 7,499,998
Mark Rothera(3)	31,213	$ 268,796
Frank E. Thomas(4)	11,614	$ 100,000
James A. Geraghty(5)	42,973	$ 370,000
Joanne T. Beck, Ph.D.(6)	11,614	$ 100,000
Marc Dunoyer(7)	46,457	$ 400,000
Charles A. Rowland, Jr.(8)	11,614	$ 100,000

(1) Consists of (i) 580,720 shares of Series C convertible preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,613,240 shares of Series C convertible preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,613,240 shares of Series C convertible preferred shares held by Deerfield Private Design Fund IV, L.P. Deerfield Management Company is a holder of 5% or more of our outstanding ordinary shares.

(2) Scottish Mortgage Investment Trust plc is a holder of 5% or more of our outstanding ordinary shares.

(3) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

(4) Mr. Thomas is our Chief Financial Officer and Chief Business Officer.

(5) Mr. Geraghty is the chairman of our board of directors.

(6) Dr. Beck is a member of our board of directors.

(7) Mr. Dunoyer is a member of our board of directors.

(8) Mr. Rowland, Jr. is a member of our board of directors.

Agreements with shareholders

In connection with the subscriptions of our Series A, Series B and Series C convertible preferred shares, we entered into subscription and shareholder agreements containing registration rights and information rights, among other things, with certain holders of our convertible preferred shares. These shareholder agreements will terminate upon the closing of this offering, except for the registration rights granted under our investors' rights agreement, as more fully described in "Description of share capital and articles of association—Registration rights."

Agreements with our executive officers and directors

We have entered into employment agreements with certain of our executive officers and service agreements with our non-executive directors. These agreements contain customary provisions and representations, including confidentiality, non-competition, non-solicitation and inventions assignment undertakings by the executive officers. However, the enforceability of the non-competition provisions may be limited under applicable law.

Indemnification agreements

We intend to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering. These agreements and our Articles of Association require us to indemnify our directors and executive officers to the fullest extent permitted by law.

Related person transaction policy

In connection with this offering, we have adopted a written related party transactions policy that such transactions must be approved by our audit committee. This policy will become effective on the date on which the registration statement of which this prospectus is part is declared effective by the SEC. Pursuant to this policy, the audit committee has the primary responsibility for reviewing and approving or disapproving "related person transactions," which are transactions between us and related persons in which the related person has a direct or indirect material interest. For purposes of this policy, a related person will be defined as a director, executive officer, nominee for director, or greater than 5% beneficial owner of any class of our voting securities, and their immediate family members.

Principal shareholders

The following table sets forth information with respect to the beneficial ownership of Orchard Therapeutics Limited's ordinary shares as of September 30, 2018, after giving effect to our corporate reorganization, for:

- each beneficial owner of 5% or more of our outstanding ordinary shares;
- each of our directors and executive officers; and
- all of our directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules of the SEC. These rules generally attribute beneficial ownership of securities to persons who possess sole or shared voting power or investment power with respect to those securities and include ordinary shares that can be acquired within 60 days of September 30, 2018. Percentage ownership calculations are based on 69,761,485 ordinary shares outstanding as of September 30, 2018, after giving effect to the conversion of all of our convertible preferred shares into ordinary shares on a one-for-one basis and our corporate reorganization as described elsewhere in this prospectus including the 1-for-0.8003 reverse split to be effected prior to the completion of this offering.

The percentage of shares beneficially owned after completion of this offering is based on 83,094,818 ordinary shares outstanding after this offering, including 13,333,333 ordinary shares in the form of ADSs issued in connection with this offering, assuming no exercise of the underwriters' option to purchase additional ADSs.

The following table does not give effect to any ADSs that may be acquired by our directors or executive officers pursuant to our directed share program.

Except as otherwise indicated, all of the shares reflected in the table are ordinary shares and all persons listed below have sole voting and investment power with respect to the shares beneficially owned by them, subject to applicable community property laws. The information is not necessarily indicative of beneficial ownership for any other purpose.

As of September 30, 2018, 35,555,013 ordinary shares, representing 51.0% of our issued and outstanding shares, were held by 34 U.S. shareholders of record.

Except as otherwise indicated in the table below, addresses of the directors, executive officers and named beneficial owners are in care of Orchard Therapeutics Limited, 108 Cannon Street, London EC4N 6EU, United Kingdom.

Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
5% or Greater Shareholders:			
Entities affiliated with F-Prime(1)	20,407,250	29.3%	24.6
GSK(2)	12,455,252	17.9%	15.0
Entities affiliated with Deerfield Management Company(3)	4,647,500	6.7%	5.6
Scottish Mortgage Investment Trust plc(4)	3,898,325	5.6%	4.7
Executive Officers and Directors:			
Mark Rothera(5)	524,090	*	*
Frank E. Thomas(6)	9,254	*	*
Bobby Gaspar, M.D., Ph.D.(7)	831,735	1.2%	1.0
James A. Geraghty(8)	34,391	*	*
Joanne T. Beck, Ph.D.(9)	9,294	*	*

Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
Marc Dunoyer(10)	37,179	*	*
Jon Ellis, Ph.D.	—	—	—
Alex Pasteur, Ph.D.	—	—	—
Charles A. Rowland, Jr.(11)	9,294	*	*
Hong Fang Song	—	—	—
Elise Wang	—	—	—
All current directors and executive officers as a group (11 persons)(12)	1,455,277	2.1%	1.8%

* Represents beneficial ownership of less than one percent.

(1) Consists of (i) 1,000,375 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (ii) 8,003,000 of our ordinary shares issuable upon conversion of our Series A convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iii) 1,200,450 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iv) 1,000,375 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; (v) 8,003,000 shares of our ordinary shares issuable upon conversion of our Series A convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; and (vi) 1,200,450 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital Partners Healthcare Advisors Fund IV LP is the general partner of F-Prime Capital Partners Healthcare Fund IV LP. F-Prime Capital Partners Healthcare Advisors Fund IV-A LP is the general partner of F-Prime Capital Partners Healthcare Fund IV-A LP. Each of F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital Partners Healthcare Advisors Fund IV-A LP is solely managed by Impresa Management LLC, the managing member of its general partner and investment manager. Each of the entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address of these entities is 245 Summer Street, Boston, MA 02210.

(2) Consists of 12,445,252 of our ordinary shares issuable upon conversion of our Series B-2 convertible preferred shares held by GSK. The board of directors of GSK may be deemed to share voting and investment authority over the shares held by GSK. The address of GSK is 980 Great West Road, Brentford, Middlesex, London TW8 9GS, UK.

(3) Consists of (i) 464,750 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,091,375 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,091,375 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Private Design Fund IV, L.P. Deerfield Mgmt, L.P. is the general partner of Deerfield Special Situations Fund, L.P. Deerfield Mgmt III, L.P. is the general partner of Deerfield Private Design Fund III, L.P. Deerfield Mgmt IV, L.P. is the general partner of Deerfield Private Design Fund IV, L.P. (collectively with Deerfield Special Situations Fund, L.P. and Deerfield Private Design Fund III, L.P., the "Deerfield Funds"). Deerfield Management Company, L.P. is the investment manager of each of the Deerfield Funds. Mr. James E. Flynn is the sole member of the general partner of each of Deerfield Mgmt, L.P., Deerfield Mgmt III, L.P., Deerfield Mgmt. IV, L.P. and Deerfield Management Company, L.P. Deerfield Mgmt, L.P. may be deemed to beneficially own the shares held by Deerfield Special Situations Fund, L.P. Deerfield Mgmt III, L.P. may be deemed to beneficially own the shares held by Deerfield Private Design III, L.P. Deerfield Mgmt IV, L.P. may be deemed to beneficially own the shares held by Deerfield Private Design Fund IV, L.P. Each of Deerfield Management Company, L.P. and Mr. James E. Flynn may be deemed to beneficially own the securities held by the Deerfield Funds. The address of the Deerfield Funds is 780 Third Avenue, 37th Floor, New York, NY 10017.

(4) Consists of (i) 3,201,200 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares and (ii) 697,125 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Scottish Mortgage Investment Trust plc ("SMIT"). As investment manager for SMIT, Baillie Gifford & Co. may be deemed to share voting and investment control over the shares held by SMIT. SMIT is a publicly traded company. The address for SMIT is c/o Baillie Gifford & Co., Calton Square, 1 Greenside Row, Edinburgh EH1 3AN, United Kingdom.

(5) Consists of (i) 39,825 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares, (ii) 24,979 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares and (iii) 459,286 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.

(6) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.

(7) Consists of (i) 417,319 of our ordinary shares and (ii) 414,416 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.

(8) Consists of 34,391 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.

(9) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.

(10) Consists of 37,179 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.

(11) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.

(12) Consists of (i) 417,319 of our ordinary shares, (ii) 39,825 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares, (iii) 124,431 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares and (iv) 873,702 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.

Description of share capital and articles of association

The following describes our issued share capital, summarizes the material provisions of our articles of association and highlights certain differences in corporate law in the United Kingdom and the United States.

We were incorporated pursuant to the laws of England and Wales as Orchard Rx Limited in August 2018 to become a holding company for Orchard Therapeutics Limited. Pursuant to the terms of our corporate reorganization, which will be completed prior to the completion of this offering, all of the issued share capital in Orchard Therapeutics Limited will be exchanged for identical shares in Orchard Rx Limited and, as a result, Orchard Therapeutics Limited will become a wholly owned subsidiary of Orchard Rx Limited. See “Corporate reorganization” for more information.

We are registered with the Registrar of Companies in England and Wales under number 11494381, and our registered office is at 108 Cannon Street, London EC4N 6EU, United Kingdom.

Certain resolutions were passed by our shareholders prior to the completion of this offering. These include resolutions for the:

- adoption of new articles of association that will become effective upon the completion of this offering. See “—Post-IPO articles of association” below;
- general authorization of our directors for purposes of Section 551 of the Companies Act 2006 to issue shares in the company and grant rights to subscribe for or convert any securities into shares in the company up to a maximum aggregate nominal amount of £113,023,851.50 for a period of five years; and
- empowering of our directors pursuant to Section 570 of Companies Act 2006 to issue equity securities for cash pursuant to the Section 551 authority referred to above as if the statutory preemption rights under Section 561(1) of the Companies Act 2006 did not apply to such allotments.

Issued share capital

As of September 30, 2018, and prior to the 1-for-0.8003 reverse split of our ordinary and convertible preferred shares to be effected prior to completion of this offering, the issued share capital of Orchard Therapeutics Limited was 11,986,245 ordinary shares and 75,182,984 convertible preferred shares. The nominal value of our ordinary shares and convertible preferred shares is £0.00001 per share and each issued ordinary share and convertible preferred share is fully paid. The issued share capital consisted of 11,986,245 ordinary shares, 21,000,000 Series A convertible preferred shares, 21,198,154 Series B convertible preferred shares, 15,563,230 Series B-2 convertible preferred shares and 17,421,600 Series C convertible preferred shares. As of September 30, 2018, the issued share capital of Orchard Rx Limited was 1 ordinary share of £0.00001. Following the exchange of shares of Orchard Therapeutics Limited for shares of Orchard Rx Limited, the issued share capital of Orchard Rx Limited is the same number of ordinary and convertible preferred shares in the same classes. As of the completion of the corporate reorganization and this offering, including the 1-for-0.8003 reverse split of our ordinary and convertible preferred shares, in each case, assuming an initial public offering price of $15.00 per ADS, the midpoint of the range set forth on the cover page of this prospectus, our issued share capital will be 83,094,818 ordinary shares.

Ordinary shares

In accordance with our Articles of Association to be in effect upon the completion of this offering, the following summarizes the rights of holders of our ordinary shares:

- each holder of our ordinary shares is entitled to one vote per ordinary share on all matters to be voted on by shareholders generally;
- the holders of the ordinary shares shall be entitled to receive notice of, attend, speak and vote at our general meetings; and
- holders of our ordinary shares are entitled to receive such dividends as are recommended by our directors and declared by our shareholders.

Registered shares

We are required by the Companies Act 2006 to keep a register of our shareholders. Under English law, the ordinary shares are deemed to be issued when the name of the shareholder is entered in our share register. The share register therefore is prima facie evidence of the identity of our shareholders, and the shares that they hold. The share register generally provides limited, or no, information regarding the ultimate beneficial owners of our ordinary shares. Our share register is maintained by our registrar. Holders of our ADSs will not be treated as one of our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see “Description of American depositary shares” in this prospectus.

Under the Companies Act 2006, we must enter an allotment of shares in our share register as soon as practicable and in any event within two months of the allotment. We will perform all procedures necessary to update the share register to reflect the ordinary shares being sold in this offering, including updating the share register with the number of ordinary shares to be issued to the depositary upon the closing of this offering. We also are required by the Companies Act 2006 to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

We, any of our shareholders or any other affected person may apply to the court for rectification of the share register if:

- the name of any person, without sufficient cause, is wrongly entered in or omitted from our register of members; or
- there is a default or unnecessary delay in entering on the register the fact of any person having ceased to be a member or on which we have a lien, provided that such delay does not prevent dealings in the shares taking place on an open and proper basis.

Preemptive rights

English law generally provides shareholders with preemptive rights when new shares are issued for cash; however, it is possible for the articles of association, or shareholders in general meeting, to exclude preemptive rights. Such an exclusion of preemptive rights may be for a maximum

period of up to five years from the date of adoption of the articles of association, if the exclusion is contained in the articles of association, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). In October 2018, our shareholders approved the exclusion of preemptive rights for a period of five years from the date of approval, which exclusion will need to be renewed upon expiration (i.e., at least every five years) to remain effective, but may be sought more frequently for additional five-year terms (or any shorter period). In October 2018, our shareholders approved the exclusion of preemptive rights for the allotment of ordinary shares in connection with this offering.

Registration rights

Upon the completion of this offering, the holders of 60,168,900 shares of our ordinary shares issuable upon the conversion of our Series A, Series B, Series B-2 and Series C convertible preferred shares, will be entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of an investment and shareholders' agreement between us and holders of our convertible preferred shares. The investment and shareholders' agreement includes demand registration rights, short-form registration rights and piggyback registration rights.

Demand registration rights

Beginning 180 days after the effective date of this registration statement, the holders of 60,168,900 shares of our ordinary shares issuable upon the conversion of convertible preferred shares upon closing of this offering are entitled to demand registration rights. Under the terms of the investment and shareholders' agreement, we will be required, upon the written request of holders of a majority of these securities to file a registration statement and use best efforts to effect the registration of all or a portion of these shares for public resale. We are required to effect only two registrations pursuant to this provision of the investment and shareholders' agreement.

Short-form registration rights

Pursuant to the investment and shareholders' agreement, if we are eligible to file a registration statement on Form F-3 or Form S-3, upon the written request of holders of a majority of these securities at an aggregate offer price of at least $5.0 million, we will be required to effect a registration of such shares. We are required to effect only two registrations in any twelve month period pursuant to this provision of the investment and shareholders' agreement. The right to have such shares registered on Form F-3 or Form S-3 is further subject to other specified conditions and limitations.

Piggyback registration rights

Pursuant to the investment and shareholders' agreement, if we register any of our securities either for our own account or for the account of other security holders, other than in connection with our initial public offering or a registration for any employee benefit plan, corporate reorganization, or the offer or sale of debt securities, the holders of these shares are entitled to include their shares in the registration. Subject to certain exceptions contained in the investment and shareholders' agreement, we and the underwriters may limit the number of shares included

in the underwritten offering to the number of shares which we and the underwriters determine in our sole discretion will not jeopardize the success of the offering.

Indemnification

Our investors' rights agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of registration rights

The registration rights granted under the investment and shareholders' agreement will terminate on the earliest of (i) a deemed liquidation event, as defined in our Articles of Association, and (ii) the fifth anniversary of the completion of this offering.

Post-IPO articles of association

Our Articles of Association, or the Articles, were approved by our shareholders prior to the completion of this offering and were adopted with effect from the completion of the offering. A summary of the terms of the Articles is set out below. The summary below is not a complete copy of the terms of the Articles.

The Articles contain no specific restrictions on our purpose and therefore, by virtue of section 31(1) of the Companies Act 2006, our purpose is unrestricted.

The Articles contain, among other things, provisions to the following effect:

Share capital

Our share capital will consist of ordinary shares. We may issue shares with such rights or restrictions as may be determined by ordinary resolution, including shares which are to be redeemed, or are liable to be redeemed at our option or the holder of such shares.

Voting

The shareholders have the right to receive notice of, and to vote at, our general meetings. Each shareholder who is present in person (or, being a corporation, by representative) at a general meeting on a show of hands has one vote and, on a poll, every such holder who is present in person (or, being a corporation, by representative) or by proxy has one vote in respect of every share held by him.

Variation of rights

Whenever our share capital is divided into different classes of shares, the special rights attached to any class may be varied or abrogated either with the consent in writing of the holders of three-fourths in nominal value of the issued shares of that class or with the sanction of a special resolution passed at a general meeting of the holders of the shares of that class and may be so varied and abrogated whilst the company is a going concern.

Dividends

We may, subject to the provisions of the Companies Act 2006 and the Articles, by ordinary resolution from time to time declare dividends to be paid to shareholders not exceeding the amount recommended by our board of directors. Subject to the provisions of the Companies Act 2006, in so far as, in the board of directors' opinions, our profits justify such payments, the board of directors may pay interim dividends on any class of our shares.

Any dividend unclaimed after a period of 12 years from the date such dividend was declared or became payable shall, if the board of directors resolve, be forfeited and shall revert to us. No dividend or other moneys payable on or in respect of a share shall bear interest as against us.

Liquidation Preference

On a distribution of assets on a liquidation, the surplus assets remaining after payment of liabilities shall be distributed among the holders of ordinary shares pro rata to the number of ordinary shares held.

Transfer of ordinary shares

Each member may transfer all or any of his shares which are in certificated form by means of an instrument of transfer in any usual form or in any other form which the board of directors may approve. Each member may transfer all or any of his shares which are in uncertificated form by means of a "relevant system" (i.e., the CREST System) in such manner provided for, and subject as provided in, the CREST Regulations.

The Board may, in its absolute discretion, refuse to register a transfer of certificated shares unless:

(i) it is for a share which is fully paid up;

(ii) it is for a share upon which the company has no lien;

(iii) it is only for one class of share;

(iv) it is in favor of a single transferee or no more than four joint transferees;

(v) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the board of directors to be exempt from stamp duty; and

(vi) it is delivered for registration to the registered office of the company (or such other place as the board of directors may determine), accompanied (except in the case of a transfer by a person to whom the company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the board of directors may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

The board of directors may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the CREST Regulations and the CREST System.

Allotment of shares and preemption rights

Subject to the Companies Act 2006 and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the board of directors may determine (including shares which are to be redeemed, or are liable to be redeemed at the option of the company or the holder of such shares).

In accordance with section 551 of the Companies Act 2006, the board of directors may be generally and unconditionally authorized to exercise all the powers of the company to allot shares up to an aggregate nominal amount equal to the amount stated in the relevant ordinary resolution authorizing such allotment. The authorities referred to above were included in the special resolution passed in October 2018 and remain in force at the date of this prospectus.

The provisions of section 561 of the Companies Act 2006 (which confer on shareholders rights of preemption in respect of the allotment of equity securities which are paid up in cash) apply to the company except to the extent disapplied by special resolution of the company. Such preemption rights have been disapplied pursuant to the special resolution passed in October 2018.

Alteration of share capital

The company may by ordinary resolution consolidate or divide all of its share capital into shares of larger nominal value than its existing shares, or cancel any shares which, at the date of the ordinary resolution, have not been taken or agreed to be taken by any person and diminish the amount of its share capital by the nominal amount of shares so cancelled or sub-divide its shares, or any of them, into shares of smaller nominal value.

The company may, in accordance with the Companies Act 2006, reduce or cancel its share capital or any capital redemption reserve or share premium account in any manner and with and subject to any conditions, authorities and consents required by law.

Board of directors

Unless otherwise determined by the company by ordinary resolution, the number of directors (other than any alternate directors) shall not be less than two, but there shall be no maximum number of directors.

Subject to the Articles and the Companies Act 2006, the company may by ordinary resolution appoint a person who is willing to act as a director and the board of directors shall have power at any time to appoint any person who is willing to act as a director, in both cases either to fill a vacancy or as an addition to the existing board of directors.

The Articles of Association provide that upon completion of this offering, our board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution.

Subject to the provisions of the Articles, the board of directors may regulate their proceedings as they deem appropriate. A director may, and the secretary at the request of a director shall, call a meeting of the directors.

The quorum for a meeting of the board of directors shall be fixed from time to time by a decision of the board of directors, but it must never be less than two and unless otherwise fixed, it is two.

Questions and matters requiring resolution arising at a meeting shall be decided by a majority of votes of the participating directors, with each director having one vote. In the case of an equality of votes, the chairman will only have a casting vote or second vote when an acquisition has been completed.

Directors shall be entitled to receive such remuneration as the board shall determine for their services to the company as directors, and for any other service which they undertake for the company provided that the aggregate fees payable to the directors must not exceed £250,000 per annum. The directors shall also be entitled to be paid all reasonable expenses properly incurred by them in connection with their attendance at meetings of shareholders or class meetings, board of director or committee meetings or otherwise in connection with the exercise of their powers and the discharge of their responsibilities in relation to the company.

The board of directors may, in accordance with the requirements in the Articles, authorize any matter proposed to them by any director which would, if not authorized, involve a director breaching his duty under the Companies Act 2006, to avoid conflicts of interests.

A director seeking authorization in respect of such conflict shall declare to the board of directors the nature and extent of his interest in a conflict as soon as is reasonably practicable. The director shall provide the board with such details of the matter as are necessary for the board to decide how to address the conflict together with such additional information as may be requested by the board.

Any authorization by the board of directors will be effective only if:

(i) to the extent permitted by the Companies Act 2006, the matter in question shall have been proposed by any director for consideration in the same way that any other matter may be proposed to the directors under the provisions of the Articles;

(ii) any requirement as to the quorum for consideration of the relevant matter is met without counting the conflicted director and any other conflicted director; and

(iii) the matter is agreed to without the conflicted director voting or would be agreed to if the conflicted director’s and any other interested director’s vote is not counted.

Subject to the provisions of the Companies Act 2006, every director, secretary or other officer of the company (other than an auditor) is entitled to be indemnified against all costs, charges, losses, damages and liabilities incurred by him in the actual purported exercise or discharge of his duties or exercise of his powers or otherwise in relation to them.

General meetings

The company must convene and hold general meetings in accordance with the Companies Act. Under the Companies Act 2006, an annual general meeting must be called by notice of at least 21 days and a general meeting must be called by notice of at least 14 days.

No business shall be transacted at any general meeting unless a quorum is present when the meeting proceeds to business, but the absence of a quorum shall not preclude the choice or appointment of a chairman of the meeting which shall not be treated as part of the business of the meeting. Save as otherwise provided by the Articles, two shareholders present in person or by proxy and entitled to vote shall be a quorum for all purposes.

Borrowing Powers

Subject to the Articles and the Companies Act 2006, the board of directors may exercise all of the powers of the company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the company or of any third party.

Capitalization of profits

The directors may, if they are so authorized by an ordinary resolution of the shareholders, decide to capitalize any undivided profits of the company (whether or not they are available for distribution), or any sum standing to the credit of the company's share premium account or capital redemption reserve. The directors may also, subject to the aforementioned ordinary resolution, appropriate any sum which they so decide to capitalize to the persons who would have been entitled to it if it were distributed by way of dividend and in the same proportions.

Uncertificated shares

Subject to the Companies Act 2006, the board of directors may permit title to shares of any class to be issued or held otherwise than by a certificate and to be transferred by means of a "relevant system" (i.e., the CREST System) without a certificate.

The board of directors may take such steps as it sees fit in relation to the evidencing of and transfer of title to uncertificated shares, any records relating to the holding of uncertificated shares and the conversion of uncertificated shares to certificated shares, or vice-versa.

The company may by notice to the holder of an uncertificated share, require that share to be converted into certificated form.

The board of directors may take such other action that the board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of an uncertified share or otherwise to enforce a lien in respect of it.

Other relevant laws and regulations

Mandatory bid

(i) The Takeover Code will apply to the company for so long as its central management and control is considered to be in the United Kingdom. Under the Takeover Code, where:

(a) any person, together with persons acting in concert with him, acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares in which he is already interested, and in which persons acting in concert with him are interested) carry 30% or more of the voting rights of a company; or

(b) any person who, together with persons acting in concert with him, is interested in shares which in the aggregate carry not less than 30% of the voting rights of a company but does not hold shares carrying more than 50% of such voting rights and such person, or any person acting in concert with him, acquires an interest in any other shares which increases the percentage of shares carrying voting rights in which he is interested;

such person shall, except in limited circumstances, be obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights. Offers for different classes of equity share capital must be comparable; the Takeover Panel should be consulted in advance in such cases.

(ii) An offer under Rule 9 of the Takeover Code must be in cash and at the highest price paid for any interest in the shares by the person required to make an offer or any person acting in concert with him during the 12 months prior to the announcement of the offer.

(iii) Under the Takeover Code, a "concert party" arises where persons acting together pursuant to an agreement or understanding (whether formal or informal and whether or not in writing) actively cooperate, through the acquisition by them of an interest in shares in a company, to obtain or consolidate control of the company. "Control" means holding, or aggregate holdings, of an interest in shares carrying 30% or more of the voting rights of the company, irrespective of whether the holding or holdings give *de facto* control.

Squeeze-out

(i) Under sections 979 to 982 of the Companies Act 2006, if an offeror were to acquire, or unconditionally contract to acquire, not less than 90% of the ordinary shares of the company, it could then compulsorily acquire the remaining 10%. It would do so by sending a notice to outstanding shareholders telling them that it will compulsorily acquire their shares, provided that no such notice may be served after the end of: (a) the period of three months beginning with the day after the last day on which the offer can be accepted; or (b) if earlier, and the offer is not one to which section 943(1) of the Companies Act 2006 applies, the period of six months beginning with the date of the offer.

(ii) Six weeks following service of the notice, the offeror must send a copy of it to the company together with the consideration for the ordinary shares to which the notice relates, and an instrument of transfer executed on behalf of the outstanding shareholder(s) by a person appointed by the offeror.

(iii) The company will hold the consideration on trust for the outstanding shareholders.

Sell-out

(i) Sections 983 to 985 of the Companies Act 2006 also give minority shareholders in the company a right to be bought out in certain circumstances by an offeror who has made a takeover offer. If a takeover offer relating to all the ordinary shares of the company is made at any time before the end of the period within which the offer could be accepted and the offeror held or had agreed to acquire not less than 90% of the ordinary shares, any holder of shares to which the offer related who had not accepted the offer could by a written communication to the offeror require it to acquire those shares. The offeror is required to give any shareholder notice of his right to be bought out within one month of that right arising. The offeror may impose a time limit on the rights of minority shareholders to be bought out, but that period cannot end less than three months after the end of the acceptance period, or, if longer a period of three months from the date of the notice.

(ii) If a shareholder exercises his rights, the offeror is bound to acquire those shares on the terms of the offer or on such other terms as may be agreed.

Differences in corporate law

The applicable provisions of the Companies Act 2006 differ from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of certain differences between the provisions of the Companies Act 2006 applicable to us and the General Corporation Law of the State of Delaware relating to shareholders' rights and protections. This summary is not intended to be a complete discussion of the respective rights and it is qualified in its entirety by reference to Delaware law and English law.

	England and Wales	**Delaware**
Number of Directors	Under the Companies Act 2006, a public limited company must have at least two directors and the number of directors may be fixed by or in the manner provided in a company's articles of association.	Under Delaware law, a corporation must have at least one director and the number of directors shall be fixed by or in the manner provided in the bylaws.
Removal of Directors	Under the Companies Act 2006, shareholders may remove a director without cause by an ordinary resolution (which is passed by a simple majority of those voting in person or by proxy at a general meeting) irrespective of any provisions of any service contract the director has with the company, provided 28 clear days' notice of the resolution has been given to the company and its shareholders. On receipt of notice of an intended resolution to remove a director, the company must forthwith send a copy of the notice to the director concerned. Certain other procedural requirements	Under Delaware law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (i) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board of directors is classified, stockholders may effect such removal only for cause, or (ii) in the case of a corporation having cumulative voting, if less than the entire board of directors is to be removed, no director may be

	England and Wales	Delaware
	under the Companies Act 2006 must also be followed, such as allowing the director to make representations against his or her removal either at the meeting or in writing.	removed without cause if the votes cast against his removal would be sufficient to elect him if then cumulatively voted at an election of the entire board of directors, or, if there are classes of directors, at an election of the class of directors of which he is a part.
Vacancies on the Board of Directors	Under English law, the procedure by which directors, other than a company's initial directors, are appointed is generally set out in a company's articles of association, provided that where two or more persons are appointed as directors of a public limited company by resolution of the shareholders, resolutions appointing each director must be voted on individually.	Under Delaware law, vacancies and newly created directorships may be filled by a majority of the directors then in office (even though less than a quorum) or by a sole remaining director unless (i) otherwise provided in the certificate of incorporation or bylaws of the corporation or (ii) the certificate of incorporation directs that a particular class of stock is to elect such director, in which case a majority of the other directors elected by such class, or a sole remaining director elected by such class, will fill such vacancy.
Annual General Meeting	Under the Companies Act 2006, a public limited company must hold an annual general meeting in each six-month period following the company's annual accounting reference date.	Under Delaware law, the annual meeting of stockholders shall be held at such place, on such date and at such time as may be designated from time to time by the board of directors or as provided in the certificate of incorporation or by the bylaws.
General Meeting	Under the Companies Act 2006, a general meeting of the shareholders of a public limited company may be called by the directors. Shareholders holding at least 5% of the paid-up capital of the company carrying voting rights at general meetings (excluding any paid up capital held as treasury shares) can require the directors to call a general meeting and, if the directors fail to do so within a	Under Delaware law, special meetings of the stockholders may be called by the board of directors or by such person or persons as may be authorized by the certificate of incorporation or by the bylaws.

	England and Wales	Delaware
	certain period, may themselves convene a general meeting.	
Notice of General Meetings	Under the Companies Act 2006, at least 21 days' notice must be given for an annual general meeting and any resolutions to be proposed at the meeting. Subject to a company's articles of association providing for a longer period, at least 14 days' notice is required for any other general meeting of a public limited company. In addition, certain matters, such as the removal of directors or auditors, require special notice, which is 28 days' notice. The shareholders of a company may in all cases consent to a shorter notice period, the proportion of shareholders' consent required being 100% of those entitled to attend and vote in the case of an annual general meeting and, in the case of any other general meeting, a majority in number of the members having a right to attend and vote at the meeting, being a majority who together hold not less than 95% in nominal value of the shares giving a right to attend and vote at the meeting.	Under Delaware law, unless otherwise provided in the certificate of incorporation or bylaws, written notice of any meeting of the stockholders must be given to each stockholder entitled to vote at the meeting not less than ten nor more than 60 days before the date of the meeting and shall specify the place, date, hour and purpose or purposes of the meeting.
Proxy	Under the Companies Act 2006, at any meeting of shareholders, a shareholder may designate another person to attend, speak and vote at the meeting on their behalf by proxy.	Under Delaware law, at any meeting of stockholders, a stockholder may designate another person to act for such stockholder by proxy, but no such proxy shall be voted or acted upon after three years from its date, unless the proxy provides for a longer period. A director of a Delaware corporation may not issue a proxy representing the director's voting rights as a director.
Preemptive Rights	Under the Companies Act 2006, "equity securities," being (i) shares in the company other than shares that, with respect to dividends and capital, carry a right to participate only up to a specified amount in a distribution, referred to as "ordinary shares," or (ii) rights to subscribe for, or to convert	Under Delaware law, shareholders have no preemptive rights to subscribe to additional issues of stock or to any security convertible into such stock unless, and except to the extent that, such rights are expressly provided for in the certificate of incorporation.

	England and Wales	Delaware
	securities into, ordinary shares, proposed to be allotted for cash must be offered first to the existing equity shareholders in the company in proportion to the respective nominal value of their holdings, unless an exception applies or a special resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise in each case in accordance with the provisions of the Companies Act.	
Authority to Allot	Under the Companies Act 2006, the directors of a company must not allot shares or grant rights to subscribe for or convert any security into shares unless an exception applies or an ordinary resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise, in each case in accordance with the provisions of the Companies Act.	Under Delaware law, if the corporation's charter or certificate of incorporation so provides, the board of directors has the power to authorize the issuance of stock. The board may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the corporation or any combination thereof. It may determine the amount of such consideration by approving a formula. In the absence of actual fraud in the transaction, the judgment of the directors as to the value of such consideration is conclusive.
Liability of Directors and Officers	Under the Companies Act 2006, any provision, whether contained in a company's articles of association or any contract or otherwise, that purports to exempt a director of a company, to any extent, from any liability that would otherwise attach to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company, is void. Any provision by which a company directly or indirectly provides an indemnity, to any extent, for a director of the company or of an associated company against any liability attaching to him in connection with any	Under Delaware law, a corporation's certificate of incorporation may include a provision eliminating or limiting the personal liability of a director to the corporation and its stockholders for damages arising from a breach of fiduciary duty as a director. However, no provision can limit the liability of a director for: • any breach of the director's duty of loyalty to the corporation or its stockholders; • acts or omissions not in good faith or that involve intentional

	England and Wales	Delaware
	negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act, which provides exceptions for the company to company against any liability attaching to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company of which he is a director is also void except as permitted by the Companies Act 2006, which provides exceptions for the company to (i) purchase and maintain insurance against such liability; (ii) provide a "qualifying third party indemnity," or an indemnity against liability incurred by the director to a person other than the company or an associated company or criminal proceedings in which he is convicted; and (iii) provide a "qualifying pension scheme indemnity," or an indemnity against liability incurred in connection with the company's activities as trustee of an occupational pension plan.	misconduct or a knowing violation of law; • intentional or negligent payment of unlawful dividends or stock purchases or redemptions; or • any transaction from which the director derives an improper personal benefit.
Voting Rights	Under English law, unless a poll is demanded by the shareholders of a company or is required by the chairman of the meeting or the company's articles of association, shareholders shall vote on all resolutions on a show of hands. Under the Companies Act, a poll may be demanded by (i) not fewer than five shareholders having the right to vote on the resolution; (ii) any shareholder(s) representing not less than 10% of the total voting rights of all the shareholders having the right to vote on the resolution (excluding any voting rights attaching to treasury shares); or (iii) any shareholder(s) holding shares in the company conferring a right to vote on the resolution (excluding any voting rights attaching to treasury shares) being shares on which an aggregate	Delaware law provides that, unless otherwise provided in the certificate of incorporation, each stockholder is entitled to one vote for each share of capital stock held by such stockholder.

	England and Wales	Delaware
	sum has been paid up equal to not less than 10% of the total sum paid up on all the shares conferring that right. A company's articles of association may provide more extensive rights for shareholders to call a poll. Under English law, an ordinary resolution is passed on a show of hands if it is approved by a simple majority (more than 50%) of the votes cast by shareholders present (in person or by proxy) and entitled to vote. If a poll is demanded, an ordinary resolution is passed if it is approved by holders representing a simple majority of the total voting rights of shareholders present, in person or by proxy, who, being entitled to vote on the resolution. Special resolutions require the affirmative vote of not less than 75% of the votes cast by shareholders present, in person or by proxy, at the meeting.	
Shareholder Vote on Certain Transactions	The Companies Act 2006 provides for schemes of arrangement, which are arrangements or compromises between a company and any class of shareholders or creditors and used in certain types of reconstructions, amalgamations, capital reorganizations or takeovers. These arrangements require: • the approval at a shareholders' or creditors' meeting convened by order of the court, of a majority in number representing 75% in value of the shareholders or creditors or class thereof present and voting, either in person or by proxy; and • the approval of the court.	Generally, under Delaware law, unless the certificate of incorporation provides for the vote of a larger portion of the stock, completion of a merger, consolidation, sale, lease or exchange of all or substantially all of a corporation's assets or dissolution requires: • the approval of the board of directors; and • the approval by the vote of the holders of a majority of the outstanding stock or, if the certificate of incorporation provides for more or less than one vote per share, a majority of the votes of the outstanding stock of the corporation entitled to vote on the matter.

	England and Wales	Delaware
Standard of Conduct for Directors	Under English law, a director owes various statutory and fiduciary duties to the company, including: • to act in the way he considers, in good faith, would be most likely to promote the success of the company for the benefit of its members as a whole; • to avoid a situation in which he has, or can have, a direct or indirect interest that conflicts, or possibly conflicts, with the interests of the company; • to act in accordance with the company's constitution and only exercise his powers for the purposes for which they are conferred; • to exercise independent judgment; • to exercise reasonable care, skill and diligence; • not to accept benefits from a third party conferred by reason of his being a director or doing, or not doing, anything as a director; and • to declare any interest that he has, whether directly or indirectly, in a proposed or existing transaction or arrangement with the company.	Delaware law does not contain specific provisions setting forth the standard of conduct of a director. The scope of the fiduciary duties of directors is generally determined by the courts of the State of Delaware. In general, directors have a duty to act without self-interest, on a well-informed basis and in a manner they reasonably believe to be in the best interest of the stockholders. Directors of a Delaware corporation owe fiduciary duties of care and loyalty to the corporation and to its shareholders. The duty of care generally requires that a director act in good faith, with the care that an ordinarily prudent person would exercise under similar circumstances. Under this duty, a director must inform himself of all material information reasonably available regarding a significant transaction. The duty of loyalty requires that a director act in a manner he reasonably believes to be in the best interests of the corporation. He must not use his corporate position for personal gain or advantage. In general, but subject to certain exceptions, actions of a director are presumed to have been made on an informed basis, in good faith and in the honest belief that the action taken was in the best interests of the corporation. However, this presumption may be rebutted by evidence of a breach of one of the fiduciary duties. Delaware courts have also imposed a heightened standard of conduct upon directors of a Delaware corporation who take any action designed to defeat a threatened change in control of the corporation.

	England and Wales	Delaware
		In addition, under Delaware law, when the board of directors of a Delaware corporation approves the sale or break-up of a corporation, the board of directors may, in certain circumstances, have a duty to obtain the highest value reasonably available to the shareholders.
Stockholder Suits	Under English law, generally, the company, rather than its shareholders, is the proper claimant in an action in respect of a wrong done to the company or where there is an irregularity in the company's internal management. Notwithstanding this general position, the Companies Act 2006 provides that (i) a court may allow a shareholder to bring a derivative claim (that is, an action in respect of and on behalf of the company) in respect of a cause of action arising from a director's negligence, default, breach of duty or breach of trust and (ii) a shareholder may bring a claim for a court order where the company's affairs have been or are being conducted in a manner that is unfairly prejudicial to some of its shareholders.	Under Delaware law, a stockholder may initiate a derivative action to enforce a right of a corporation if the corporation fails to enforce the right itself. The complaint must: • state that the plaintiff was a stockholder at the time of the transaction of which the plaintiff complains or that the plaintiffs shares thereafter devolved on the plaintiff by operation of law; and • allege with particularity the efforts made by the plaintiff to obtain the action the plaintiff desires from the directors and the reasons for the plaintiff's failure to obtain the action; or • state the reasons for not making the effort. Additionally, the plaintiff must remain a stockholder through the duration of the derivative suit. The action will not be dismissed or compromised without the approval of the Delaware Court of Chancery.

Stock exchange listing

We intend to apply to list our ADSs on the Nasdaq Global Market under the symbol “ORTX.”

Transfer agent and registrar of shares

Our share register will be maintained by Equiniti Limited upon the closing of this offering. The share register reflects only record owners of our ordinary shares. Holders of our ADSs will not be treated as our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the ordinary shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see “Description of American depositary shares” in this prospectus.

Description of American depositary shares

American depositary shares

Citibank, N.A., or Citibank, has agreed to act as the depositary for the ADSs. Citibank's depositary offices are located at, 388 Greenwich Street, New York, New York 10013. ADSs represent ownership interests in securities that are on deposit with the depositary. ADSs may be represented by certificates that are commonly known as American Depositary Receipts, or ADRs. The depositary typically appoints a custodian to safekeep the securities on deposit. In this case, the custodian is Citibank, N.A., London Branch, located at 25 Canada Square, Canary Wharf, London, E14 5LB, United Kingdom.

We have appointed Citibank as depositary pursuant to a deposit agreement. A copy of the deposit agreement is on file with the SEC under cover of a registration statement on Form F-6. You may obtain a copy of the deposit agreement from the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 and from the SEC's website (www.sec.gov). Please refer to registration number 333-227905 when retrieving such copy.

We are providing you with a summary description of the material terms of the ADSs and of your material rights as an owner of ADSs. Please remember that summaries by their nature lack the precision of the information summarized and that the rights and obligations of an owner of ADSs will be determined by reference to the terms of the deposit agreement and not by this summary. We urge you to review the deposit agreement in its entirety.

Each ADS represents the right to receive, and to exercise the beneficial ownership interests in, one ordinary share that is on deposit with the depositary and/or custodian. An ADS also represents the right to receive, and to exercise the beneficial interests in, any other property received by the depositary or the custodian on behalf of the owner of the ADS but that has not been distributed to the owners of ADSs because of legal restrictions or practical considerations. We and the depositary may agree to change the ADS-to-ordinary share ratio by amending the deposit agreement. This amendment may give rise to, or change, the depositary fees payable by ADS owners. The custodian, the depositary and their respective nominees will hold all deposited property for the benefit of the holders and beneficial owners of ADSs. The deposited property does not constitute the proprietary assets of the depositary, the custodian or their nominees. Beneficial ownership in the deposited property will under the terms of the deposit agreement be vested in the beneficial owners of the ADSs. The depositary, the custodian and their respective nominees will be the record holders of the deposited property represented by the ADSs for the benefit of the holders and beneficial owners of the corresponding ADSs. A beneficial owner of ADSs may or may not be the holder of ADSs. Beneficial owners of ADSs will be able to receive, and to exercise beneficial ownership interests in, the deposited property only through the registered holders of the ADSs, the registered holders of the ADSs (on behalf of the applicable ADS owners) only through the depositary, and the depositary (on behalf of the owners of the corresponding ADSs) directly, or indirectly, through the custodian or their respective nominees, in each case upon the terms of the deposit agreement.

If you become an owner of ADSs, you will become a party to the deposit agreement and therefore will be bound to its terms and to the terms of any ADR that represents your ADSs. The deposit agreement and the ADR specify our rights and obligations as well as your rights and obligations as owner of ADSs and those of the depositary. As an ADS holder you appoint the depositary to act on your behalf in certain circumstances. The deposit agreement and the ADRs

are governed by New York law. However, our obligations to the holders of ordinary shares will continue to be governed by the laws of England and Wales, which may be different from the laws of the United States.

In addition, applicable laws and regulations may require you to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. You are solely responsible for complying with such reporting requirements and obtaining such approvals. Neither the depositary, the custodian, us or any of their or our respective agents or affiliates shall be required to take any actions whatsoever on your behalf to satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

As an owner of ADSs, we will not treat you as one of our shareholders and you will not have direct shareholder rights. The depositary will hold on your behalf the shareholder rights attached to the ordinary shares underlying your ADSs. As an owner of ADSs you will be able to exercise the shareholders rights for the ordinary shares represented by your ADSs through the depositary only to the extent contemplated in the deposit agreement. To exercise any shareholder rights not contemplated in the deposit agreement you will, as an ADS owner, need to arrange for the cancellation of your ADSs and become a direct shareholder.

The manner in which you own the ADSs (e.g., in a brokerage account vs. as registered holder, or as holder of certificated vs. uncertificated ADSs) may affect your rights and obligations, and the manner in which, and extent to which, the depositary's services are made available to you. As an owner of ADSs, you may hold your ADSs either by means of an ADR registered in your name, through a brokerage or safekeeping account, or through an account established by the depositary in your name reflecting the registration of uncertificated ADSs directly on the books of the depositary (commonly referred to as the direct registration system or DRS). The direct registration system reflects the uncertificated (book-entry) registration of ownership of ADSs by the depositary. Under the direct registration system, ownership of ADSs is evidenced by periodic statements issued by the depositary to the holders of the ADSs. The direct registration system includes automated transfers between the depositary and The Depository Trust Company, or DTC, the central book-entry clearing and settlement system for equity securities in the United States. If you decide to hold your ADSs through your brokerage or safekeeping account, you must rely on the procedures of your broker or bank to assert your rights as ADS owner. Banks and brokers typically hold securities such as the ADSs through clearing and settlement systems such as DTC. The procedures of such clearing and settlement systems may limit your ability to exercise your rights as an owner of ADSs. Please consult with your broker or bank if you have any questions concerning these limitations and procedures. All ADSs held through DTC will be registered in the name of a nominee of DTC. This summary description assumes you have opted to own the ADSs directly by means of an ADS registered in your name and, as such, we will refer to you as the "holder." When we refer to "you," we assume the reader owns ADSs and will own ADSs at the relevant time.

The registration of the ordinary shares in the name of the depositary or the custodian shall, to the maximum extent permitted by applicable law, vest in the depositary or the custodian the record ownership in the applicable ordinary shares with the beneficial ownership rights and interests in such ordinary shares being at all times vested with the beneficial owners of the ADSs representing the ordinary shares. The depositary or the custodian shall at all times be entitled to exercise the beneficial ownership rights in all deposited property, in each case only on behalf of the holders and beneficial owners of the ADSs representing the deposited property.

Dividends and other distributions

As a holder of ADSs, you generally have the right to receive the distributions we make on the securities deposited with the custodian. Your receipt of these distributions may be limited, however, by practical considerations and legal limitations. Holders of ADSs will receive such distributions under the terms of the deposit agreement in proportion to the number of ADSs held as of the specified record date, after deduction the applicable fees, taxes and expenses.

Distributions of cash

Whenever we make a cash distribution for the securities on deposit with the custodian, we will deposit the funds with the custodian. Upon receipt of confirmation of the deposit of the requisite funds, the depositary will arrange for the funds received in a currency other than U.S. dollars to be converted into U.S. dollars and for the distribution of the U.S. dollars to the holders, subject to the laws and regulations of England and Wales.

The conversion into U.S. dollars will take place only if practicable and if the U.S. dollars are transferable to the United States. The depositary will apply the same method for distributing the proceeds of the sale of any property (such as undistributed rights) held by the custodian in respect of securities on deposit.

The distribution of cash will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. The depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable holders and beneficial owners of ADSs until the distribution can be effected or the funds that the depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States.

Distributions of shares

Whenever we make a free distribution of ordinary shares for the securities on deposit with the custodian, we will deposit the applicable number of ordinary shares with the custodian. Upon receipt of confirmation of such deposit, the depositary will either distribute to holders new ADSs representing the ordinary shares deposited or modify the ADS-to-ordinary shares ratio, in which case each ADS you hold will represent rights and interests in the additional ordinary shares so deposited. Only whole new ADSs will be distributed. Fractional entitlements will be sold and the proceeds of such sale will be distributed as in the case of a cash distribution.

The distribution of new ADSs or the modification of the ADS-to-ordinary share ratio upon a distribution of ordinary shares will be made net of the fees, expenses, taxes, and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes or governmental charges, the depositary may sell all or a portion of the new ordinary shares so distributed.

No such distribution of new ADSs will be made if it would violate a law (e.g., the U.S. securities laws) or if it is not operationally practicable. If the depositary does not distribute new ADSs as described above, it may sell the ordinary shares received upon the terms described in the deposit agreement and will distribute the proceeds of the sale as in the case of a distribution of cash.

Distributions of rights

Whenever we intend to distribute rights to purchase additional ordinary shares, we will give prior notice to the depositary and we will assist the depositary in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depositary will establish procedures to distribute rights to purchase additional ADSs to holders and to enable such holders to exercise such rights if it is lawful and reasonably practicable to make the rights available to holders of ADSs, and if we provide all of the documentation contemplated in the deposit agreement (such as opinions to address the lawfulness of the transaction). You may have to pay fees, expenses, taxes and other governmental charges to subscribe for the new ADSs upon the exercise of your rights. The depositary is not obligated to establish procedures to facilitate the distribution and exercise by holders of rights to purchase new ordinary shares other than in the form of ADSs.

The depositary will *not* distribute the rights to you if:

- we do not timely request that the rights be distributed to you or we request that the rights not be distributed to you;
- we fail to deliver satisfactory documents to the depositary; or
- it is not reasonably practicable to distribute the rights.

The depositary will sell the rights that are not exercised or not distributed if such sale is lawful and reasonably practicable. The proceeds of such sale will be distributed to holders as in the case of a cash distribution. If the depositary is unable to sell the rights, it will allow the rights to lapse.

Elective Distributions

Whenever we intend to distribute a dividend payable at the election of shareholders either in cash or in additional shares, we will give prior notice thereof to the depositary and will indicate whether we wish the elective distribution to be made available to you. In such case, we will assist the depositary in determining whether such distribution is lawful and reasonably practicable.

The depositary will make the election available to you only if it is reasonably practicable and if we have provided all of the documentation contemplated in the deposit agreement. In such case, the depositary will establish procedures to enable you to elect to receive either cash or additional ADSs, in each case as described in the deposit agreement.

If the election is not made available to you, you will receive either cash or additional ADSs, depending on what a shareholder in England and Wales would receive upon failing to make an election, as more fully described in the deposit agreement.

Other Distributions

Whenever we intend to distribute property other than cash, ordinary shares or rights to purchase additional ordinary shares, we will notify the depositary in advance and will indicate whether we wish such distribution to be made to you. If so, we will assist the depositary in determining whether such distribution to holders is lawful and reasonably practicable.

If it is reasonably practicable to distribute such property to you and if we provide all of the documentation contemplated in the deposit agreement, the depositary will distribute the property to the holders in a manner it deems practicable.

The distribution will be made net of fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes and governmental charges, the depositary may sell all or a portion of the property received.

The depositary will *not* distribute the property to you and will sell the property if:

- we do not request that the property be distributed to you or if we ask that the property not be distributed to you; or
- we do not deliver satisfactory documents to the depositary; or
- the depositary determines that all or a portion of the distribution to you is not reasonably practicable.

The proceeds of such a sale will be distributed to holders as in the case of a cash distribution.

Redemption

Whenever we decide to redeem any of the ordinary shares on deposit with the custodian, we will notify the depositary in advance. If it is practicable and if we provide all of the documentation contemplated in the deposit agreement, the depositary will provide notice of the redemption to the holders.

The custodian will be instructed to surrender the ordinary shares being redeemed against payment of the applicable redemption price. The depositary will convert the redemption funds received into U.S. dollars upon the terms of the deposit agreement and will establish procedures to enable holders to receive the net proceeds from the redemption upon surrender of their ADSs to the depositary. You may have to pay fees, expenses, taxes and other governmental charges upon the redemption of your ADSs. If less than all ADSs are being redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as the depositary may determine.

Changes affecting ordinary shares

The ordinary shares held on deposit for your ADSs may change from time to time. For example, there may be a change in nominal or par value, split-up, cancellation, consolidation, or any other reclassification of such ordinary shares or a recapitalization, reorganization, merger, consolidation, or sale of assets of our company.

If any such change were to occur, your ADSs would, to the extent permitted by law, represent the right to receive the property received or exchanged in respect of the ordinary shares held on deposit. The depositary may in such circumstances deliver new ADSs to you, amend the deposit agreement, the ADRs and the applicable Registration Statement(s) on Form F-6, call for the exchange of your existing ADSs for new ADSs and take any other actions that are appropriate to reflect as to the ADSs the change affecting the ordinary shares. If the depositary may not lawfully distribute such property to you, the depositary may sell such property and distribute the net proceeds to you as in the case of a cash distribution.

Issuance of ADSs upon deposit of ordinary shares

Upon completion of this offering, the ordinary shares being offered pursuant to this prospectus will be deposited by us with the custodian. Upon receipt of confirmation of such deposit, the depositary will issue ADSs to the underwriters named in this prospectus.

After the closing of this offering, the depositary may create ADSs on your behalf if you or your broker deposit ordinary shares with the custodian. The depositary will deliver these ADSs to the person you indicate only after you pay any applicable issuance fees and any charges and taxes payable for the transfer of the ordinary shares to the custodian. Your ability to deposit ordinary shares and receive ADSs may be limited by the legal considerations in the United States and England and Wales applicable at the time of deposit.

The issuance of ADSs may be delayed until the depositary or the custodian receives confirmation that all required approvals have been given and that the ordinary shares have been duly transferred to the custodian. The depositary will only issue ADSs in whole numbers.

When you make a deposit of ordinary shares, you will be responsible for transferring good and valid title to the depositary. As such, you will be deemed to represent and warrant that:

- the ordinary shares are duly authorized, validly issued, fully paid, non-assessable, and legally obtained;
- all preemptive (and similar) rights, if any, with respect to such ordinary shares have been validly waived or exercised;
- you are duly authorized to deposit the ordinary shares;
- the ordinary shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage, or adverse claim, and are not, and the ADSs issuable upon such deposit will not be, “restricted securities” (as defined in the deposit agreement);
- the ordinary shares presented for deposit have not been stripped of any rights or entitlements; and
- the deposit of shares does not violate any applicable provision of English law.

If any of the representations or warranties are incorrect in any way, we and the depositary may, at your cost and expense, take any and all actions necessary to correct the consequences of the misrepresentations.

Transfer, combination and split up of ADRs

As an ADR holder, you will be entitled to transfer, combine or split up your ADRs and the ADSs evidenced thereby. For transfers of ADRs, you will have to surrender the ADRs to be transferred to the depositary and also must:

- ensure that the surrendered ADR is properly endorsed or otherwise in proper form for transfer;
- provide such proof of identity and genuineness of signatures as the depositary deems appropriate;
- provide any transfer stamps required by the State of New York or the United States; and
- pay all applicable fees, charges, expenses, taxes, and other government charges payable by ADR holders pursuant to the terms of the deposit agreement, upon the transfer of ADRs.

To have your ADRs either combined or split up, you must surrender the ADRs in question to the depositary with your request to have them combined or split up, and you must pay all applicable fees, charges and expenses payable by ADR holders, pursuant to the terms of the deposit agreement, upon a combination or split up of ADRs.

Withdrawal of ordinary shares upon cancellation of ADSs

As a holder, you will be entitled to present your ADSs to the depositary for cancellation and then receive the corresponding number of underlying ordinary shares at the custodian's offices. Your ability to withdraw the ordinary shares held in respect of the ADSs may be limited by the legal consideration in the United States and England and Wales applicable at the time of withdrawal. In order to withdraw the ordinary shares represented by your ADSs, you will be required to pay to the depositary the fees for cancellation of ADSs and any charges and taxes payable upon the transfer of the ordinary shares. You assume the risk for delivery of all funds and securities upon withdrawal. Once canceled, the ADSs will not have any rights under the deposit agreement.

If you hold ADSs registered in your name, the depositary may ask you to provide proof of identity and genuineness of any signature and such other documents as the depositary may deem appropriate before it will cancel your ADSs. The withdrawal of the ordinary shares represented by your ADSs may be delayed until the depositary receives satisfactory evidence of compliance with all applicable laws and regulations. Please keep in mind that the depositary will only accept ADSs for cancellation that represent a whole number of securities on deposit.

You will have the right to withdraw the securities represented by your ADSs at any time except as a result of:

- temporary delays that may arise because (i) the transfer books for the ordinary shares or ADSs are closed, or (ii) ordinary shares are immobilized on account of a shareholders' meeting or a payment of dividends;
- obligations to pay fees, taxes and similar charges;
- restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit; and
- other circumstances specifically contemplated by Section I.A.(I) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time)

The deposit agreement may not be modified to impair your right to withdraw the ordinary shares represented by your ADSs except to comply with mandatory provisions of law.

Voting rights

As a holder, you generally have the right under the deposit agreement to instruct the depositary to exercise the voting rights for the ordinary shares represented by your ADSs. The voting rights of holders of ordinary shares are described in "Description of share capital and articles of association—Articles of association" in this prospectus.

At our request, the depositary will distribute to you any notice of shareholders' meeting received from us together with information explaining how to instruct the depositary to exercise the voting rights of the ordinary shares represented by ADSs. In lieu of distributing such materials, the depositary bank may distribute to holders of ADSs instructions on how to retrieve such materials upon request.

If the depositary timely receives voting instructions from a holder of ADSs, it will endeavor to vote (or cause the custodian to vote) the securities (in person or by proxy) represented by the holder's ADSs as follows:

- *In the event of voting by show of hands*, the depositary will vote (or cause the custodian to vote) all ordinary shares represented by ADSs in accordance with the voting instructions received from a majority of holders of ADSs who provide timely voting instructions.
- In the event of voting by poll, the depositary will vote (or cause the custodian to vote) the ordinary shares represented by ADSs in accordance with the voting instructions received from the holders of ADSs.

Securities for which no voting instructions have been received will not be voted (except as otherwise contemplated in the deposit agreement). Please note that the ability of the depositary to carry out voting instructions may be limited by practical and legal limitations and the terms of the securities on deposit. We cannot assure you that you will receive voting materials in time to enable you to return voting instructions to the depositary in a timely manner.

Fees and charges

As an ADS holder, you will be required to pay the following fees under the terms of the deposit agreement:

Service	Fee
Issuance of ADSs (e.g., an issuance of ADS upon a deposit of ordinary shares or upon a change in the ADS(s)-to-ordinary shares ratio), excluding ADS issuances as a result of distributions of ordinary shares	Up to $0.05 per ADS issued
Cancellation of ADSs (e.g., a cancellation of ADSs for delivery of deposited property or upon a change in the ADS(s)-to-ordinary shares ratio)	Up to $0.05 per ADS cancelled
Distribution of cash dividends or other cash distributions (e.g., upon a sale of rights and other entitlements)	Up to $0.05 per ADS held
Distribution of ADSs pursuant to (i) share dividends or other free share distributions, or (ii) exercise of rights to purchase additional ADSs	Up to $0.05 per ADS held
Distribution of securities other than ADSs or rights to purchase additional ADSs (e.g., upon a spin-off)	Up to $0.05 per ADS held
ADS Services	Up to $0.05 per ADS held on the applicable record date(s) established by the depositary

As an ADS holder you will also be responsible to pay certain charges such as:

- taxes (including applicable interest and penalties) and other governmental charges;

- the registration fees as may from time to time be in effect for the registration of ordinary shares on the share register and applicable to transfers of ordinary shares to or from the name of the custodian, the depositary, or any nominees upon the making of deposits and withdrawals, respectively;
- certain cable, telex and facsimile transmission and delivery expenses;
- the expenses and charges incurred by the depositary in the conversion of foreign currency;
- the fees and expenses incurred by the depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to ordinary shares, ADSs and ADRs; and
- the fees and expenses incurred by the depositary, the custodian or any nominee in connection with the servicing or delivery of deposited property.

ADS fees and charges payable upon (i) the issuance of ADSs, and (ii) the cancellation of ADSs are charged to the person for whom the ADSs are issued (in the case of ADS issuances) and to the person for whom ADSs are cancelled (in the case of ADS cancellations). In the case of ADSs issued by the depositary into DTC, the ADS issuance and cancellation fees and charges may be deducted from distributions made through DTC, and may be charged to the DTC participant(s) receiving the ADSs being issued or the DTC participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the beneficial owner(s) and will be charged by the DTC participant(s) to the account of the applicable beneficial owner(s) in accordance with the procedures and practices of the DTC participants as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are charged to the holders as of the applicable ADS record date. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, holders as of the ADS record date will be invoiced for the amount of the ADS fees and charges and such ADS fees and charges may be deducted from distributions made to holders of ADSs. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC participants in accordance with the procedures and practices prescribed by DTC and the DTC participants in turn charge the amount of such ADS fees and charges to the beneficial owners for whom they hold ADSs.

In the event of refusal to pay the depositary fees, the depositary may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary fees from any distribution to be made to the ADS holder. Certain depositary fees and charges (such as the ADS services fee) may become payable shortly after the closing of the ADS offering. Note that the fees and charges you may be required to pay may vary over time and may be changed by us and by the depositary. You will receive prior notice of such changes. The depositary may reimburse us for certain expenses incurred by us in respect of the ADR program, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as we and the depositary agree from time to time.

Amendments and termination

We may agree with the depositary to modify the deposit agreement at any time without your consent. We undertake to give holders 30 days' prior notice of any modifications that would

materially prejudice any of their substantial rights under the deposit agreement. We will not consider to be materially prejudicial to your substantial rights any modifications or supplements that are reasonably necessary for the ADSs to be registered under the Securities Act or to be eligible for book-entry settlement, in each case without imposing or increasing the fees and charges you are required to pay. In addition, we may not be able to provide you with prior notice of any modifications or supplements that are required to accommodate compliance with applicable provisions of law.

You will be bound by the modifications to the deposit agreement if you continue to hold your ADSs after the modifications to the deposit agreement become effective. The deposit agreement cannot be amended to prevent you from withdrawing the ordinary shares represented by your ADSs (except as permitted by law).

We have the right to direct the depositary to terminate the deposit agreement. Similarly, the depositary may in certain circumstances on its own initiative terminate the deposit agreement. In either case, the depositary must give notice to the holders at least 30 days before termination. Until termination, your rights under the deposit agreement will be unaffected.

Termination

After termination, the depositary will continue to collect distributions received (but will not distribute any such property until you request the cancellation of your ADSs) and may sell the securities held on deposit. After the sale, the depositary will hold the proceeds from such sale and any other funds then held for the holders of ADSs in a non-interest bearing account. At that point, the depositary will have no further obligations to holders other than to account for the funds then held for the holders of ADSs still outstanding (after deduction of applicable fees, taxes and expenses).

In connection with the termination of the deposit agreement, the depositary may, independently and without the need for any action by us, make available to holders a means to withdraw the ordinary shares and other deposited securities represented by their ADSs and to direct the deposit of such ordinary shares and other deposited securities into an unsponsored ADS program established by the depositary, upon such terms and conditions as the depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored ADS program under the Securities Act, and to receipt by the depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the depositary.

Books of depositary

The depositary will maintain ADS holder records at its depositary office. You may inspect such records at such office during regular business hours but solely for the purpose of communicating with other holders in the interest of business matters relating to the ADSs and the deposit agreement.

The depositary will maintain in New York facilities to record and process the issuance, cancellation, combination, split-up and transfer of ADSs. These facilities may be closed from time to time, to the extent not prohibited by law.

Transmission of notices, reports and proxy soliciting material

The depositary will make available for your inspection at its office all communications that it receives from us as a holder of deposited securities that we make generally available to holders of deposited securities. Subject to the terms of the deposit agreement, the depositary will send you copies of those communications or otherwise make those communications available to you if we ask it to.

Limitations on obligations and liabilities

The deposit agreement limits our obligations and the depositary's obligations to you. Please note the following:

- We and the depositary are obligated only to take the actions specifically stated in the deposit agreement without negligence or bad faith.
- The depositary disclaims any liability for any failure to carry out voting instructions, for any manner in which a vote is cast or for the effect of any vote, provided it acts in good faith and in accordance with the terms of the deposit agreement.
- The depositary disclaims any liability for any failure to determine the lawfulness or practicality of any action, for the content of any document forwarded to you on our behalf or for the accuracy of any translation of such a document, for the investment risks associated with investing in ordinary shares, for the validity or worth of the ordinary shares, for any tax consequences that result from the ownership of ADSs, for the credit-worthiness of any third party, for allowing any rights to lapse under the terms of the deposit agreement, for the timeliness of any of our notices or for our failure to give notice.
- We and the depositary will not be obligated to perform any act that is inconsistent with the terms of the deposit agreement.
- We and the depositary disclaim any liability if we or the depositary are prevented or forbidden from or subject to any civil or criminal penalty or restraint on account of, or delayed in, doing or performing any act or thing required by the terms of the deposit agreement, by reason of any provision, present or future of any law or regulation, or by reason of present or future provision of any provision of our Articles of Association or any provision of or governing the securities on deposit, or by reason of any act of God or war or other circumstances beyond our control.
- We and the depositary disclaim any liability by reason of any exercise of, or failure to exercise, any discretion provided for in the deposit agreement or in our Articles of Association or in any provisions of or governing the securities on deposit.
- We and the depositary further disclaim any liability for any action or inaction in reliance on the advice or information received from legal counsel, accountants, any person presenting ordinary shares for deposit, any holder of ADSs or authorized representatives thereof, or any other person believed by either of us in good faith to be competent to give such advice or information.
- We and the depositary also disclaim liability for the inability by a holder to benefit from any distribution, offering, right or other benefit that is made available to holders of ordinary shares but is not, under the terms of the deposit agreement, made available to you.

- We and the depositary may rely without any liability upon any written notice, request or other document believed to be genuine and to have been signed or presented by the proper parties.
- We and the depositary also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.
- No disclaimer of any Securities Act liability is intended by any provision of the deposit agreement.

Nothing in the deposit agreement gives rise to a partnership or joint venture, or establishes a fiduciary relationship, among us, the depositary bank and you as ADS holder.

Nothing in the deposit agreement precludes Citibank (or its affiliates) from engaging in transactions in which parties adverse to us or the ADS owners have interests, and nothing in the deposit agreement obligates Citibank to disclose those transactions, or any information obtained in the course of those transactions, to us or to the ADS owners, or to account for any payment received as part of those transactions.

Taxes

You will be responsible for the taxes and other governmental charges payable on the ADSs and the ordinary shares represented by the ADSs. We, the depositary and the custodian may deduct from any distribution the taxes and governmental charges payable by holders and may sell any and all property on deposit to pay the taxes and governmental charges payable by holders. You will be liable for any deficiency if the sale proceeds do not cover the taxes that are due.

The depositary may refuse to issue ADSs, to deliver, transfer, split and combine ADRs or to release securities on deposit until all taxes and charges are paid by the applicable holder. The depositary and the custodian may take reasonable administrative actions to obtain tax refunds and reduced tax withholding for any distributions on your behalf. However, you may be required to provide to the depositary and to the custodian proof of taxpayer status and residence and such other information as the depositary and the custodian may require to fulfill legal obligations. You are required to indemnify us, the depositary and the custodian for any claims with respect to taxes based on any tax benefit obtained for you.

Foreign currency conversion

The depositary will arrange for the conversion of all foreign currency received into U.S. dollars if such conversion is practical, and it will distribute the U.S. dollars in accordance with the terms of the deposit agreement. You may have to pay fees and expenses incurred in converting foreign currency, such as fees and expenses incurred in complying with currency exchange controls and other governmental requirements.

If the conversion of foreign currency is not practical or lawful, or if any required approvals are denied or not obtainable at a reasonable cost or within a reasonable period, the depositary may take the following actions in its discretion:

- Convert the foreign currency to the extent practical and lawful and distribute the U.S. dollars to the holders for whom the conversion and distribution is lawful and practical.
- Distribute the foreign currency to holders for whom the distribution is lawful and practical.
- Hold the foreign currency (without liability for interest) for the applicable holders.

Governing Law/Waiver of Jury Trial

The deposit agreement, the ADRs and ADSs will be interpreted in accordance with the laws of the State of New York. The rights of holders of ordinary shares (including ordinary shares represented by ADSs) are governed by the laws of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, YOU IRREVOCABLY WAIVE YOUR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT, THE ADRs AND ADSs AGAINST US AND/OR THE DEPOSITARY. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable in the facts and circumstances of that case in accordance with applicable case law. However, you will not be deemed by agreeing to the terms of the deposit agreement to have waived our or the depositary's compliance with U.S. federal securities laws and the rules and regulations promulgated thereunder.

Shares and ADSs eligible for future sale

Prior to this offering, there has been no public market for our ordinary shares or ADSs. Upon completion of this offering, and assuming no exercise of the underwriters' option to purchase additional ADSs, we will have 83,094,818 ADSs outstanding, representing 83,094,818 ordinary shares. Future sales of ADSs in the public market after this offering, and the availability of ADSs for future sale, could adversely affect the market price of the ADSs prevailing from time to time. Some of our ordinary shares are subject to contractual and legal restrictions on resale as described below. There may be sales of substantial amounts of our ADSs or ordinary shares in the public market after such restrictions lapse, which could adversely affect prevailing market prices of our ADSs.

We expect 13,333,333 ADSs, or 15,333,332 ADSs if the underwriters exercise in full their option to purchase additional ADSs, sold in this offering will be freely transferable without restriction, except for any shares purchased by one or more of our existing "affiliates," as that term is defined in Rule 144 under the Securities Act. We expect approximately 69,761,485 ADSs will be subject to the contractual 180-day lock-up period described below. This may adversely affect the prevailing market price of our ADSs and our ability to raise equity capital in the future.

Rule 144

In general, persons who have beneficially owned restricted ordinary shares for at least six months, and any affiliate of the company who owns either restricted or unrestricted securities, are entitled to sell their securities without registration with the SEC under an exemption from registration provided by Rule 144 under the Securities Act.

Non-Affiliates

Any person who is not deemed to have been one of our affiliates at the time of, or at any time during the three months preceding, a sale may sell an unlimited number of restricted securities under Rule 144 if:

- the restricted securities have been held for at least six months, including the holding period of any prior owner other than one of our affiliates;
- we have been subject to the Exchange Act periodic reporting requirements for at least 90 days before the sale; and
- we are current in our Exchange Act reporting at the time of sale.

Any person who is not deemed to have been an affiliate of ours at the time of, or at any time during the three months preceding, a sale and has held the restricted securities for at least one year, including the holding period of any prior owner other than one of our affiliates, will be entitled to sell an unlimited number of restricted securities without regard to the length of time we have been subject to Exchange Act periodic reporting or whether we are current in our Exchange Act reporting.

Affiliates

Persons seeking to sell restricted securities who are our affiliates at the time of, or any time during the three months preceding, a sale, would be subject to the restrictions described above.

They are also subject to additional restrictions, by which such person would be required to comply with the manner of sale and notice provisions of Rule 144 and would be entitled to sell within any three-month period only that number of securities that does not exceed the greater of either of the following:

- 1% of the number of ordinary shares then outstanding, which will equal approximately 830,948 shares immediately after the closing of this offering based on the number of ordinary shares outstanding as of September 30, 2018; or
- the average weekly trading volume of our ordinary shares in the form of ADSs on the Nasdaq Global Market during the four calendar weeks preceding the filing of a notice on Form 144 with respect to the sale.

Additionally, persons who are our affiliates at the time of, or any time during the three months preceding, a sale may sell unrestricted securities under the requirements of Rule 144 described above, without regard to the six-month holding period of Rule 144, which does not apply to sales of unrestricted securities.

Rule 701

Rule 701 under the Securities Act, as in effect on the date of this prospectus, permits resales of shares in reliance upon Rule 144 but without compliance with certain restrictions of Rule 144, including the holding period requirement. Most of our employees, executive officers or directors who purchased shares under a written compensatory plan or contract may be entitled to rely on the resale provisions of Rule 701, but all holders of Rule 701 shares are required to wait until 90 days after the date of this prospectus before selling their shares. However, substantially all Rule 701 shares are subject to lock-up agreements as described below and in the section of this prospectus titled “Underwriting” and will become eligible for sale upon the expiration of the restrictions set forth in those agreements.

Regulation S

Regulation S provides generally that sales made in offshore transactions are not subject to the registration or prospectus delivery requirements of the Securities Act.

Lock-up agreements

All of our directors, executive officers and the holders of substantially all of our ordinary shares have agreed, subject to limited exceptions, not to offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our ADSs, ordinary shares or such other securities for a period of 180 days after the date of this prospectus, without the prior written consent of J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC. See “Underwriting.”

Material income tax considerations

The following summary contains a description of material U.K. and U.S. federal income tax consequences of the acquisition, ownership and disposition of our ordinary shares or ADSs. This summary should not be considered a comprehensive description of all the tax considerations that may be relevant to the decision to acquire ordinary shares or ADSs in this offering.

Material U.S. federal income tax considerations for U.S. holders

The following is a description of the material U.S. federal income tax consequences to the U.S. Holders described below of owning and disposing of our ordinary shares or ADSs. It is not a comprehensive description of all tax considerations that may be relevant to a particular person's decision to acquire securities. This discussion applies only to a U.S. Holder that is an initial purchaser of the ordinary shares or ADSs pursuant to the offering and that holds our ordinary shares or ADSs as a capital asset for tax purposes (generally, property held for investment). In addition, it does not describe all of the tax consequences that may be relevant in light of a U.S. Holder's particular circumstances, including state and local tax consequences, estate tax consequences, alternative minimum tax consequences, the potential application of the Medicare contribution tax, and tax consequences applicable to U.S. Holders subject to special rules, such as:

- banks, insurance companies, and certain other financial institutions;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- dealers or traders in securities who use a mark-to-market method of tax accounting;
- persons holding ordinary shares or ADSs as part of a hedging transaction, "straddle," wash sale, conversion transaction or integrated transaction or persons entering into a constructive sale with respect to ordinary shares or ADSs;
- persons whose "functional currency" for U.S. federal income tax purposes is not the U.S. dollar;
- brokers, dealers or traders in securities, commodities or currencies;
- tax-exempt entities or government organizations;
- S corporations, partnerships, or other entities or arrangements classified as partnerships for U.S. federal income tax purposes;
- regulated investment companies or real estate investment trusts;
- persons who acquired our ordinary shares or ADSs pursuant to the exercise of any employee stock option or otherwise as compensation; and
- persons holding our ordinary shares or ADSs in connection with a trade or business, permanent establishment, or fixed base outside the United States.

If an entity that is classified as a partnership for U.S. federal income tax purposes holds ordinary shares or ADSs, the U.S. federal income tax treatment of a partner will generally depend on the status of the partner and the activities of the partnership. Partnerships holding ordinary shares or ADSs and partners in such partnerships are encouraged to consult their tax advisers as to the particular U.S. federal income tax consequences of holding and disposing of ordinary shares or ADSs.

The discussion is based on the Code, administrative pronouncements, judicial decisions, final, temporary and proposed Treasury Regulations, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as of the date hereof, changes to any of which may affect the tax consequences described herein—possibly with retroactive effect.

A "U.S. Holder" is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

(i) An individual who is a citizen or individual resident of the United States;

(ii) a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;

(iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

(iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

We do not believe that we were a PFIC in the 2017 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a "controlled foreign corporation" for any taxable year (see discussion below in "Controlled foreign corporation considerations"), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a "deemed sale" election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the "deemed sale" election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder's ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any "excess distribution" the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any "excess distribution" such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute "marketable" securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder's holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder's holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and

- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or "excess distribution" cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF Election. In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are "marketable." Ordinary shares or ADSs will be marketable if they are "regularly traded" on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, and you are a holder of ADSs, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder's adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder's adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves "marketable." As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax

advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an annual report containing such information as the U.S. Treasury may require. A U.S. Holder's failure to file the annual report will cause the statute of limitations for such U.S. Holder's U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the annual report, and, unless such failure is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder's entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE YOU TO CONSULT YOUR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs.

Controlled foreign corporation considerations

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income each year for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of certain types of income earned by the CFC, including "Subpart F income," "global intangible low-taxed income" and certain other income generated by the CFC, even if the CFC has made no distributions to its shareholders. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in the CFC may be required to classify a portion of such gain as dividend income rather than capital gain (see discussion below in "Taxation of distributions" regarding the tax treatment of dividend income). A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation.

We believe that we were not a CFC in the 2017 taxable year, though we have not made a determination regarding our CFC status in the current taxable year, and we may become a CFC in a subsequent taxable year. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. In addition, recent changes to the attribution rules relating to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. It is possible that, following this offering, a shareholder treated as a U.S. person for U.S. federal income tax purposes will acquire, directly or indirectly, enough shares to be treated as a Ten Percent Shareholder. We also believe that immediately following this offering we may have certain shareholders that are Ten Percent Shareholders for U.S. federal income tax purposes. U.S. Holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. Holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Taxation of distributions

Subject to the discussion above under "PFIC rules," distributions paid on ordinary shares or ADSs, other than certain pro rata distributions of ordinary shares or ADSs, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we may not calculate our earnings and profits under U.S. federal income tax principles, we expect that distributions generally will be reported to U.S. Holders as dividends. Subject to applicable limitations and the discussions above regarding concerns expressed by the U.S. Treasury, dividends paid to certain non-corporate U.S. Holders may be taxable at preferential rates applicable to "qualified dividend income" if we are a "qualified foreign corporation" and certain other requirements are met. However, the qualified dividend income treatment may not apply if we are treated as a PFIC with respect to the U.S. Holder. The amount of the dividend will be treated as foreign-source dividend income to U.S. Holders and will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Dividends will generally be included in a U.S. Holder's income on the date of the U.S. Holder's receipt of the dividend. The amount of any dividend income paid in foreign currency will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual or constructive receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt. Such gain or loss would generally be treated as U.S.-source ordinary income or loss. The amount of any distribution of property other than cash (and other than certain pro rata distributions of ordinary shares or ADSs or rights to acquire ordinary shares or ADSs) will be the fair market value of such property on the date of distribution.

For foreign tax credit limitation purposes, our dividends will generally be treated as passive category income. Because no U.K. income taxes will be withheld from dividends on ordinary shares or ADSs, there will be no creditable foreign taxes associated with any dividends that a U.S. Holder will receive. The rules governing foreign tax credits are complex and U.S. Holders should therefore consult their tax advisers regarding the effect of the receipt of dividends for foreign tax credit limitation purposes.

Sale or other taxable disposition of ordinary shares and ADSs

Subject to the discussion above under "PFIC rules," gain or loss realized on the sale or other taxable disposition of ordinary shares or ADSs will be capital gain or loss, and will be long-term capital gain or loss if the U.S. Holder held the ordinary shares or ADSs for more than one year. The amount of the gain or loss will equal the difference between the U.S. Holder's tax basis in the ordinary shares or ADSs disposed of and the amount realized on the disposition, in each case as determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

If the consideration received by a U.S. Holder is not paid in U.S. dollars, the amount realized will be the U.S. dollar value of the payment received determined by reference to the spot rate of exchange on the date of the sale or other disposition. However, if the ordinary shares or ADSs are treated as traded on an "established securities market" and you are either a cash basis taxpayer or an accrual basis taxpayer that has made a special election (which must be applied

consistently from year to year and cannot be changed without the consent of the IRS), you will determine the U.S. dollar value of the amount realized in a non-U.S. dollar currency by translating the amount received at the spot rate of exchange on the settlement date of the sale. If you are an accrual basis taxpayer that is not eligible to or does not elect to determine the amount realized using the spot rate on the settlement date, you will recognize foreign currency gain or loss to the extent of any difference between the U.S. dollar amount realized on the date of sale or disposition and the U.S. dollar value of the currency received at the spot rate on the settlement date.

Information reporting and backup withholding

Payments of dividends and sales proceeds that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) the U.S. Holder is a corporation or other exempt recipient or (ii) in the case of backup withholding, the U.S. Holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding on a duly executed Form W-9 or otherwise establishes an exemption.

Backup withholding is not an additional tax. The amount of any backup withholding from a payment to a U.S. Holder will be allowed as a credit against the U.S. Holder's U.S. federal income tax liability and may entitle the U.S. Holder to a refund, provided that the required information is timely furnished to the IRS.

Information with respect to foreign financial assets

Certain U.S. Holders who are individuals (and, under regulations, certain entities) may be required to report information relating to the ordinary shares or ADSs, subject to certain exceptions (including an exception for ordinary shares or ADSs held in accounts maintained by certain U.S. financial institutions), by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. Such U.S. Holders who fail to timely furnish the required information may be subject to a penalty. Additionally, if a U.S. Holder does not file the required information, the statute of limitations with respect to tax returns of the U.S. Holder to which the information relates may not close until three years after such information is filed. U.S. Holders should consult their tax advisers regarding their reporting obligations with respect to their ownership and disposition of the ordinary shares or ADSs.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HMRC published practice applying as at the date of this prospectus (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from U.K. taxation. It is written on the basis that the company is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under "Material U.S. federal income tax considerations for U.S. Holders."

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and in the case of individuals, domiciled or

deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment, branch or agency (or equivalent) in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the ADSs or underlying ordinary shares (where the dividends are regarded for U.K. tax purposes as that person's own income). It is assumed that for the purposes of this guide that a holder of an ADS is the beneficial owner of the underlying ordinary share and any dividend income for U.K. direct tax purposes.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- brokers or dealers in securities or persons who hold ADSs otherwise than as an investment;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a permanent establishment, branch or agency to which the ADSs are attributable.

Dividend income is treated as the top slice of the total income chargeable to U.K. income tax. An individual U.K. Holder who receives a dividend in the 2018/2019 tax year will be entitled to a tax-free allowance of £2,000. Dividend income in excess of this tax-free allowance will be charged at 7.5% for basic rate taxpayers, 32.5% for higher rate taxpayers, and 38.1% for additional rate taxpayers.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate U.K. Holders should not be subject to U.K. corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, although certain conditions must be met. If the conditions for the exemption are not satisfied, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19%).

Chargeable gains

A disposal or deemed disposal of ADSs by a U.K. Holder may, depending on the U.K. Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of U.K. capital gains tax and corporation tax on chargeable gains.

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the applicable rate will be 20% (2018/2019). For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to U.K. capital gains tax on such disposal, the applicable rate would be 10% (2018/2019), save to the extent that any capital gains exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (2018/2019).

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax (currently 19%) would apply.

A holder of ADSs which is not resident for tax purposes in the U.K. should not normally be liable to U.K. capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs, unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation in the United Kingdom through a permanent establishment, branch or agency to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the U.K. for a period of less than five years and who disposes of ADSs during that period may be liable on his or her return to the U.K. to U.K. tax on any capital gain realized (subject to any available exemption or relief).

Stamp duty and stamp duty reserve tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Ordinary Shares

No U.K. stamp duty or stamp duty reserve tax, or SDRT, is payable on the issue of the underlying ordinary shares in the company.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

An unconditional agreement to transfer ordinary shares to, or to a nominee or agent for, a person whose business is or includes the issue of depositary receipts or the provision of clearance services will generally be subject to SDRT (and, where the transfer is effected by a written instrument, stamp duty) at a higher rate of 1.5% of the amount or value of the consideration given for the transfer unless the clearance service has made and maintained an election under section 97A of the U.K. Finance Act 1986, or a section 97A election. It is understood that HMRC regards the facilities of DTC as a clearance service for these purposes and we are not aware of any section 97A election having been made by the DTC.

Based on current published HMRC practice following recent case law in respect of the European Council Directives 69/335/EEC and 2009/7/EC, or the Capital Duties Directives, no SDRT is generally payable where the transfer of ordinary shares to a clearance service or depositary receipt system outside the European Union is an integral part of an issue of share capital (although the relevant judgment refers to transfers which are integral to the raising of capital). In addition, a recent Court of Justice of the European Union judgment (Air Berlin plc v HMRC (2017)) held on the relevant facts that the Capital Duties Directives preclude the taxation of a transfer of legal title to shares for the sole purpose of listing those shares on a stock exchange which does not impact the beneficial ownership of the shares, but, as yet, the U.K. domestic law and HMRC's published practice remain unchanged and, accordingly, we anticipate that amounts on account of SDRT will continue to be collected by the depositary receipt issuer or clearance service. Holders of ordinary shares should consult their own independent professional advisers before incurring or reimbursing the costs of such a 1.5% SDRT charge. Any stamp duty or SDRT payable on a transfer of ordinary shares to a depositary receipt system or clearance service will in practice generally be paid by the participants in the clearance service or depositary receipt system.

Transfers of ADSs

No U.K. stamp duty will in practice be payable on a written instrument transferring an ADS provided that the instrument of transfer is executed and remains at all times outside the United Kingdom. Where these conditions are not met, the transfer of, or agreement to transfer, an ADS could, depending on the circumstances, attract a charge to U.K. stamp duty at the rate of 0.5% of the value of the consideration.

No SDRT will be payable in respect of an agreement to transfer an ADS.

Underwriting

We are offering the ADSs described in this prospectus through a number of underwriters. J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC are acting as joint book-running managers of the offering and as representatives of the underwriters. We have entered into an underwriting agreement with the underwriters. Subject to the terms and conditions of the underwriting agreement, we have agreed to sell to the underwriters, and each underwriter has severally agreed to purchase, at the public offering price less the underwriting discounts and commissions set forth on the cover page of this prospectus, the number of ADSs listed next to its name in the following table:

Name	Number of ADSs
J.P. Morgan Securities LLC	
Goldman Sachs & Co. LLC	
Cowen and Company, LLC	
Wedbush Securities Inc.	
Total	13,333,333

The underwriters are committed to purchase all the ADSs offered by us if they purchase any ADSs. The underwriting agreement also provides that if an underwriter defaults, the purchase commitments of non-defaulting underwriters may also be increased or the offering may be terminated.

The underwriters propose to offer the ADSs directly to the public at the initial public offering price set forth on the cover page of this prospectus and to certain dealers at that price less a concession not in excess of $ per ADS. Any such dealers may resell ADSs to certain other brokers or dealers at a discount of up to $ per ADS from the initial public offering price. After the initial offering of the ADSs to the public, if all of the ADSs are not sold at the initial public offering price, the underwriters may change the offering price and the other selling terms. Sales of ADSs made outside of the United States may be made by affiliates of the underwriters. The offering of the ADSs by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

The underwriters have an option to buy up to 1,999,999 additional ADSs from us to cover sales of ADSs by the underwriters which exceed the number of ADSs specified in the table above. The underwriters have 30 days from the date of this prospectus to exercise this option to purchase additional ADSs. If any ADSs are purchased with this option to purchase additional ADSs, the underwriters will purchase ADSs in approximately the same proportion as shown in the table above. If any additional ADSs are purchased, the underwriters will offer the additional ADSs on the same terms as those on which the ADSs are being offered.

The underwriting fee is equal to the public offering price per ADS less the amount paid by the underwriters to us per ADS. The underwriting fee is $ per ADS. The following table shows the per ADS and total underwriting discounts and commissions to be paid to the underwriters assuming both no exercise and full exercise of the underwriters' option to purchase additional ADSs.

	Without option to purchase additional ADSs exercise	With full option to purchase additional ADSs exercise
Per ADS	$	$
Total	$	$

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately $4.2 million.

At our request, the underwriters have reserved up to 666,666 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the initial public offering price per ADS through a directed share program, to directors, officers, employees and certain other individuals associated with us. If purchased by these persons, these ADSs will not be subject to a lock-up restriction. The number of ADSs available for sale to the general public will be reduced by the number of reserved ADSs sold to these individuals. Any reserved ADSs not purchased by these individuals will be offered by the underwriters to the general public on the same basis as the other ADSs offered pursuant to this prospectus. The directed share program will be arranged through J.P. Morgan Securities LLC.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of ADSs to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (i) offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any ADSs or securities convertible into or exchangeable or exercisable for any ADSs, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any ADSs or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of ADSs or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC for a period of 180 days after the date of this prospectus, other than the ADSs to be sold in this offering and any ADSs issued upon the exercise of options granted under our stock plans.

Our directors and executive officers, and certain of our significant shareholders have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant

to which each of these persons or entities, with limited exceptions, for a period of 180 days after the date of this prospectus, may not, without the prior written consent of J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC, (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any of our ordinary shares or ADSs or any securities exchangeable or exercisable for or convertible into our ordinary shares or ADSs, or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of our ordinary shares or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of ordinary shares or such other securities, in cash or otherwise, or (3) make any demand for or exercise any right with respect to the registration of any of our ordinary shares or any security convertible into or exercisable or exchangeable for our Ordinary Shares, in each case, subject to certain exceptions, including:

- the ADSs to be sold in this offering;
- the exchange of ordinary shares of Orchard Therapeutics Limited for equivalent equity interests in Orchard Therapeutics plc in connection with our corporate reorganization;
- the deposit of ordinary shares with the depositary, in exchange for the issuance of ADSs, or the cancellation of ADSs in exchange for the issuance of ordinary shares;
- sales or transfers of ADSs or ordinary shares acquired in this offering or in open market transactions after the consummation of this offering;
- transfers of our ordinary shares or ADSs as a bona fide gift or gifts; by will, other testamentary document or interstate succession to the legal representative, heir, beneficiary or member of the immediate family of the transferor in a transaction not involving a disposition for value; or pursuant to a court order in respect of, or by operation of law as a result of, a divorce, in a transaction not involving a disposition for value;
- transfer of our ordinary shares or ADSs to such person or such person’s immediate family members for estate planning purposes;
- transfer of our ordinary shares or ADSs to the members, limited or general partners or shareholders of such person, its direct or indirect affiliates or other entities controlled or managed by the transferor in a transaction not involving a disposition for value;
- in the case of a trust, transfer of our ordinary shares or ADSs to beneficiaries of the transferor in a transaction not involving a disposition for value;
- the receipt of our ordinary shares or ADSs by such person in connection with the conversion of outstanding convertible preferred shares upon the consummation of this offering into ordinary shares;
- the exercise of an option or other equity award to purchase our ordinary shares or ADSs, which are set to expire during the 180-day period following the date of this prospectus;
- any transfer or disposition in connection with any bona fide third-party tender offer, merger, consolidation or other similar transaction that is approved by our board of directors and made to all holders of our ordinary shares or ADSs, the result of which is that a person, or group of persons, other than the Company becomes beneficial owner of more than 50% of our voting stock; and

- the establishment of a written trading plan meeting the requirements of Rule 10b5-1 under the Exchange Act.

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act.

We will apply to have our ADSs approved for listing/quotation on Nasdaq under the symbol “ORTX”.

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling ADSs in the open market for the purpose of preventing or retarding a decline in the market price of the ADSs while this offering is in progress. These stabilizing transactions may include making short sales of the ADSs, which involves the sale by the underwriters of a greater number of ADSs than they are required to purchase in this offering, and purchasing ADSs on the open market to cover positions created by short sales. Short sales may be “covered” shorts, which are short positions in an amount not greater than the underwriters’ option to purchase additional ADSs referred to above, or may be “naked” shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional ADSs, in whole or in part, or by purchasing ADSs in the open market. In making this determination, the underwriters will consider, among other things, the price of ADSs available for purchase in the open market compared to the price at which the underwriters may purchase ADSs through the option to purchase additional ADSs. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the ADSs in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase ADSs in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the ADSs, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase ADSs in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those ADSs as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the ADSs or preventing or retarding a decline in the market price of the ADSs, and, as a result, the price of the ADSs may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on the Nasdaq Global Market, in the over-the-counter market or otherwise.

Prior to this offering, there has been no public market for our ADSs. The initial public offering price will be determined by negotiations between us and the representatives of the underwriters. In determining the initial public offering price, we and the representatives of the underwriters expect to consider a number of factors including:

- the information set forth in this prospectus and otherwise available to the representatives;
- our prospects and the history and prospects for the industry in which we compete;
- an assessment of our management;

- our prospects for future earnings;
- the general condition of the securities markets at the time of this offering;
- the recent market prices of, and demand for, publicly traded shares of generally comparable companies; and
- other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our ADSs, or that the ADSs will trade in the public market at or above the initial public offering price.

Other relationships

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future. Such investment and trading activities may involve or relate to assets, securities and/or instruments of the issuer (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the issuer. The underwriters and their affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

Selling restrictions

General

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

European economic area

In relation to each Member State of the EEA, or each, a Relevant Member State, no offer of ADSs may be made to the public in that Relevant Member State other than:

A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or

C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,

provided that no such offer of ADSs shall require us or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any ADSs or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a "qualified investor" within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any ADSs being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the ADSs acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any ADSs to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

The Company, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of ADSs in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of ADSs. Accordingly any person making or intending to make an offer in that Relevant Member State of ADSs which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriters have authorized, nor do they authorize, the making of any offer of ADSs in circumstances in which an obligation arises for the Company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression "an offer to the public" in relation to any ADSs in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the ADSs to be offered so as to enable an investor to decide to purchase or subscribe the ADSs, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression "Prospectus Directive" means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression "2010 PD Amending Directive" means Directive 2010/73/EU.

Hong Kong

The ADSs may not be offered or sold by means of any document other than (i) in circumstances that do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), or (ii) to "professional investors" within the meaning of the

Securities and Futures Ordinance (Cap.571, Laws of Hong Kong) and any rules made thereunder, or (iii) in other circumstances that do not result in the document being a “prospectus” within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), and no advertisement, invitation or document relating to the ADSs may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the laws of Hong Kong) other than with respect to ADSs that are or are intended to be disposed of only to persons outside Hong Kong or only to “professional investors” within the meaning of the Securities and Futures Ordinance (Cap. 571, Laws of Hong Kong) and any rules made thereunder.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Law of Japan, or the Financial Instruments and Exchange Law, and each underwriter has agreed that it will not offer or sell any securities, directly or indirectly, in Japan or to, or for the benefit of, any resident of Japan (which term, as used in this prospectus means any person resident in Japan, including any corporation or other entity organized under the laws of Japan) or to others for re-offering or resale, directly or indirectly, in Japan or to a resident of Japan, except pursuant to an exemption from the registration requirements of, and otherwise in compliance with, the Financial Instruments and Exchange Law and any other applicable laws, regulations and ministerial guidelines of Japan.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the ADSs may not be circulated or distributed, nor may the ADSs be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor under Section 274 of the Securities and Futures Act, Chapter 289 of Singapore, or the SFA, (ii) to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA.

Where the ADSs are subscribed or purchased under Section 275 by a relevant person that is: (a) a corporation (which is not an accredited investor) the sole business of which is to hold investments and the entire ADSs capital of which is owned by one or more individuals, each of whom is an accredited investor; or (b) a trust (where the trustee is not an accredited investor) whose sole purpose is to hold investments and each beneficiary is an accredited investor, ADSs, debentures and units of ADSs and debentures of that corporation or the beneficiaries’ rights and interest in that trust shall not be transferable for six months after that corporation or that trust has acquired the ADSs under Section 275 except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person, or any person pursuant to Section 275(1A), and in accordance with the conditions, specified in Section 275 of the SFA; (2) where no consideration is given for the transfer; or (3) by operation of law.

Switzerland

The ADSs may not be publicly offered in Switzerland and will not be listed on the SIX Swiss Exchange, or SIX, or on any other stock exchange or regulated trading facility in Switzerland. This document has been prepared without regard to the disclosure standards for issuance prospectuses under art. 652a or art. 1156 of the Swiss Code of Obligations or the disclosure standards for listing prospectuses under art. 27 ff. of the SIX Listing Rules or the listing rules of any other stock exchange or regulated trading facility in Switzerland. Neither this document, nor any other offering or marketing material relating to the ADSs or this offering, may be publicly distributed or otherwise made publicly available in Switzerland. Neither this document nor any other offering or marketing material relating to this offering, the Company, the ADSs has been or will be filed with or approved by any Swiss regulatory authority. In particular, this document will not be filed with, and the offer of ADSs will not be supervised by, the Swiss Financial Market Supervisory Authority FINMA, or FINMA, and the offer of ADSs has not been and will not be authorized under the Swiss Federal Act on Collective Investment Schemes, or CISA. The investor protection afforded to acquirers of interests in collective investment schemes under the CISA does not extend to acquirers of ADSs.

United Arab Emirates

This prospectus relates to an Exempt Offer in accordance with the Offered Securities Rules of the Dubai Financial Services Authority, or DFSA. This prospectus is intended for distribution only to persons of a type specified in the Offered Securities Rules of the DFSA. It must not be delivered to, or relied on by, any other person. The DFSA has no responsibility for reviewing or verifying any documents in connection with Exempt Offers. The DFSA has not approved this prospectus nor taken steps to verify the information set forth herein and has no responsibility for this prospectus. The ADSs to which this prospectus relates may be illiquid and/or subject to restrictions on their resale. Prospective purchasers of the ADSs offered should conduct their own due diligence on the ADSs. If you do not understand the contents of this prospectus, you should consult an authorized financial advisor.

United Kingdom

In addition, in the United Kingdom, this document is being distributed only to, and is directed only at, and any offer subsequently made may only be directed at persons who are “qualified investors” (as defined in the Prospectus Directive) (i) who have professional experience in matters relating to investments falling within Article 19 (5) of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2005, as amended (the “Order”) and/or (ii) who are high net worth companies (or persons to whom it may otherwise be lawfully communicated) falling within Article 49(2)(a) to (d) of the Order (all such persons together being referred to as “relevant persons”).

Any person in the United Kingdom that is not a relevant person should not act or rely on the information included in this document or use it as basis for taking any action. In the United Kingdom, any investment or investment activity that this document relates to may be made or taken exclusively by relevant persons. Any person in the United Kingdom that is not a relevant person should not act or rely on this document or any of its contents.

Canada

The ADSs may be sold only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions and Ongoing Registrant Obligations. Any resale of the ADSs must be made in accordance with an exemption from, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this prospectus (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory for particulars of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the representatives are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Expenses of this offering

Set forth below is an itemization of the total expenses, excluding the underwriting discounts and commissions, which are expected to be incurred in connection with the sale of ADSs in this offering. With the exception of the registration fee payable to the SEC, The Nasdaq Global Market listing fee and the filing fee payable to FINRA, all amounts are estimates.

Expense	Amount
SEC registration fee	$ 29,735
Nasdaq Global Market listing fee	225,000
FINRA filing fee	37,300
Underwriters legal fees	45,000
Printing expenses	350,000
Legal fees and expenses	2,000,000
Accounting fees and expenses	1,200,000
Miscellaneous costs	262,965
Total	$ 4,150,000

Legal matters

The validity of our ADSs and certain other matters of English law and U.S. federal law will be passed upon for us by Goodwin Procter (UK) LLP and Goodwin Procter LLP. Legal counsel to the underwriters in connection with this offering are Davis Polk & Wardwell LLP.

Experts

The consolidated financial statements of Orchard Therapeutics Limited as of December 31, 2016 and December 31, 2017 and for each of the two years in the period ended December 31, 2017 included in this prospectus have been so included in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

The registered business address of PricewaterhouseCoopers LLP is 1 Embankment Place, London, WC2N 6RH, United Kingdom.

Service of process and enforcement of liabilities

We are incorporated and currently existing under the laws of England and Wales. In addition, certain of our directors and officers reside outside of the United States and most of the assets of our non-U.S. subsidiaries are located outside of the United States. As a result, it may be difficult for investors to effect service of process on us or those persons in the United States or to enforce in the United States judgments obtained in United States courts against us or those persons based on the civil liability or other provisions of the United States securities laws or other laws.

In addition, uncertainty exists as to whether the courts of England and Wales would:

- recognize or enforce judgments of United States courts obtained against us or our directors or officers predicated upon the civil liabilities provisions of the securities laws of the United States or any state in the United States; or
- entertain original actions brought in England and Wales against us or our directors or officers predicated upon the securities laws of the United States or any state in the United States.

We have been advised by Goodwin Procter LLP that there is currently no treaty between (i) the United States and (ii) England and Wales providing for reciprocal recognition and enforcement of judgments of United States courts in civil and commercial matters (although the United States and the United Kingdom are both parties to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards) and that a final judgment for the payment of money rendered by any general or state court in the United States based on civil liability, whether predicated solely upon the United States securities laws, would not be automatically enforceable in England and Wales. We have also been advised by Goodwin Procter LLP that any final and conclusive monetary judgment for a definite sum obtained against us in United States courts would be treated by the courts of England and Wales as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that:

- the relevant U.S. court had jurisdiction over the original proceedings according to English conflicts of laws principles at the time when proceedings were initiated;
- England and Wales courts had jurisdiction over the matter on enforcement and we either submitted to such jurisdiction or were resident or carrying on business within such jurisdiction and were duly served with process;
- the U.S. judgment was final and conclusive on the merits in the sense of being final and unalterable in the court that pronounced it and being for a definite sum of money;
- the judgment given by the courts was not in respect of penalties, taxes, fines or similar fiscal or revenue obligations (or otherwise based on a U.S. law that an English court considers to relate to a penal, revenue or other public law);
- the judgment was not procured by fraud;
- recognition or enforcement of the judgment in England and Wales would not be contrary to public policy or the Human Rights Act 1998;
- the proceedings pursuant to which judgment was obtained were not contrary to natural justice;
- the U.S. judgment was not arrived at by doubling, trebling or otherwise multiplying a sum assessed as compensation for the loss or damages sustained and not being otherwise in breach

of Section 5 of the U.K. Protection of Trading Interests Act 1980, or is a judgment based on measures designated by the Secretary of State under Section 1 of that Act;

- there is not a prior decision of an English court or the court of another jurisdiction on the issues in question between the same parties; and
- the English enforcement proceedings were commenced within the limitation period.

Whether these requirements are met in respect of a judgment based upon the civil liability provisions of the United States securities laws, including whether the award of monetary damages under such laws would constitute a penalty, is an issue for the court making such decision.

Subject to the foregoing, investors may be able to enforce in England and Wales judgments in civil and commercial matters that have been obtained from U.S. federal or state courts. Nevertheless, we cannot assure you that those judgments will be recognized or enforceable in England and Wales.

If an English court gives judgment for the sum payable under a U.S. judgment, the English judgment will be enforceable by methods generally available for this purpose. These methods generally permit the English court discretion to prescribe the manner of enforcement. In addition, it may not be possible to obtain an English judgment or to enforce that judgment if the judgment debtor is or becomes subject to any insolvency or similar proceedings, or if the judgment debtor has any set-off or counterclaim against the judgment creditor. Also note that, in any enforcement proceedings, the judgment debtor may raise any counterclaim that could have been brought if the action had been originally brought in England unless the subject of the counterclaim was in issue and denied in the U.S. proceedings.

Where you can find additional information

We have filed with the SEC a registration statement (including amendments and exhibits to the registration statement) on Form F-1 under the Securities Act. A related registration statement on Form F-6 has been filed with the SEC to register the ADSs. This prospectus, which forms a part of the registration statement, does not contain all of the information included in the registration statement and the exhibits and schedules to the registration statement. Certain information is omitted and you should refer to the registration statement and its exhibits and schedules for that information. If a document has been filed as an exhibit to the registration statement, we refer you to the copy of the document that has been filed. Each statement in this prospectus relating to a document filed as an exhibit is qualified in all respects by the filed exhibit.

You may review a copy of the registration statement, including exhibits and any schedule filed therewith, and obtain copies of such materials at the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet website (http://www.sec.gov) that contains reports, proxy and information statements and other information regarding issuers, like us, that file electronically with the SEC.

Upon completion of this offering, we will be subject to the information reporting requirements of the Exchange Act applicable to foreign private issuers. Accordingly, we will be required to file reports and other information with the SEC, including annual reports on Form 20-F and reports on Form 6-K. Those reports may be inspected without charge at the locations described above. As a foreign private issuer, we will be exempt from the rules under the Exchange Act related to the furnishing and content of proxy statements, and our officers, directors and principal shareholders will be exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act. In addition, we will not be required under the Exchange Act to file periodic reports and financial statements with the SEC as frequently or as promptly as U.S. companies whose securities are registered under the Exchange Act.

We maintain a corporate website at www.orchard-tx.com. Information contained in, or that can be accessed through, our website is not a part of, and shall not be incorporated by reference into, this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

Index to the financial statements

All historical share and per share data included in these financial statements exclude the impact of the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The pro forma earnings per share data does give effect to the split.

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Orchard Therapeutics Limited

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Orchard Therapeutics Limited and its subsidiaries as of December 31, 2017 and 2016, and the related consolidated statements of operations and comprehensive loss, of convertible preferred shares and shareholders' (deficit) equity and of cash flows for each of the two years in the period ended December 31, 2017, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016, and the results of their operations and their cash flows for each of the two years in the period ended December 31, 2017 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP
PricewaterhouseCoopers LLP
Reading, United Kingdom
August 6, 2018, except for the effects of the revision discussed in Note 14 to the consolidated financial statements, as to which the date is October 23, 2018

We have served as the Company's auditor since 2018.

Orchard Therapeutics Limited
Consolidated balance sheets
(In thousands, except share and per share amounts)

	December 31	
	2016	**2017**
Assets		
Current assets:		
Cash	$ 3,497	$ 89,856
Other receivables	33	1,247
Prepaid expenses and other current assets	448	3,118
Total current assets	3,978	94,221
Non-current assets:		
Property and equipment, net	184	2,713
Other long-term receivables	121	360
Total non-current assets	305	3,073
Total assets	$ 4,283	$ 97,294
Liabilities, convertible preferred shares and shareholders' (deficit) equity		
Current liabilities:		
Accounts payable	$ 698	$ 3,891
Accrued expenses and other current liabilities	1,715	6,864
Tranche obligations	1,402	—
Total current liabilities	3,815	10,755
Other long-term liabilities	22	134
Total liabilities	3,837	10,889
Commitments and contingencies (*Note 11*)		
Convertible preferred shares: £0.00001 par value; 21,000,000 shares authorized as of December 31, 2016; 14,000,000 shares issued and outstanding as of December 31, 2016; aggregate liquidation preference of $17,222 as of December 31, 2016.	16,970	—
Shareholders' (deficit) equity:		
Convertible preferred shares, £0.00001 par value; 42,198,154 shares authorized as of December 31, 2017; 41,581,513 shares issued and outstanding as of December 31, 2017; aggregate liquidation preference of $139,954 as of December 31, 2017.	—	134,069
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,000 and £675,413 of shares at December 31, 2016 and 2017, respectively; 9,305,175 and 11,154,720 shares issued and outstanding at December 31, 2016 and 2017, respectively.	—	—
Additional paid-in capital	3,404	7,610
Accumulated other comprehensive (loss) income	(271)	4,127
Accumulated deficit	(19,657)	(59,401)
Total shareholders' (deficit) equity	(16,524)	86,405
Total liabilities, convertible preferred shares and shareholders' (deficit) equity	$ 4,283	$ 97,294

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited
Consolidated statements of operations and comprehensive loss
(In thousands, except share and per share amounts)

	Year ended December 31,	
	2016	**2017**
Operating expenses:		
Research and development	$ 16,206	$ 32,527
General and administrative	2,997	5,985
Total operating expenses	19,203	38,512
Loss from operations	(19,203)	(38,512)
Other income (expense):		
Interest income	3	—
Change in fair value of tranche obligations	289	—
Other expense	(154)	(1,179)
Total other income (expense), net	138	(1,179)
Net loss before income tax	(19,065)	(39,691)
Income tax expense	(20)	(53)
Net loss attributable to ordinary shareholders	$ (19,085)	$ (39,744)
Other comprehensive (loss) income		
Foreign currency translation adjustment	(271)	4,398
Total comprehensive loss	$ (19,356)	$ (35,346)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.15)	$ (3.58)
Weighted average number of ordinary shares outstanding, basic and diluted	8,872,333	11,086,808
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	$ (2.69)	$ (4.48)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	7,100,528	8,872,768
Supplemental pro forma net loss per share attributable to ordinary shares, basic and diluted (unaudited)		$ (1.24)
Supplemental pro forma weighted average number of ordinary shares outstanding, basis and diluted (unaudited)		32,056,206

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited
Consolidated statement of convertible preferred shares and shareholders' (deficit) equity
(In thousands, except share amounts)

	Convertible preferred shares		Convertible preferred shares		Ordinary shares		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2015	**—**	**$ —**	**—**	**$ —**	**3,370,175**	**$ —**	**$ —**	**$ —**	**$ (572)**	**$ (572)**
Issuance of convertible preferred shares, net of issuance costs	14,000,000	16,970	—	—	—	—	—	—	—	—
Conversion of ordinary shares to deferred shares	—	—	—	—	(100,000)	—		—	—	—
Share-based compensation expense	—	—	—	—		—	204	—	—	204
Ordinary shares committed to be issued as part of license agreements	—	—	—	—	—	—	465	—	—	465
Ordinary shares issued as part of license agreements	—	—	—	—	6,035,000	—	2,735	—	—	2,735
Foreign currency translation adjustment	—	—	—	—	—	—	—	(271)	—	(271)
Net loss	—	—	—	—	—	—	—	—	(19,085)	(19,085)
Balance at December 31, 2016	**14,000,000**	**$ 16,970**	**—**	**$ —**	**9,305,175**	**$ —**	**$ 3,404**	**$ (271)**	**$ (19,657)**	**$(16,524)**
Issuance of convertible preferred shares, net of issuance costs	18,359,625	66,981	—	—	—	—	—	—	—	—
Reclassification of convertible preferred shares from temporary equity to permanent equity	(32,359,625)	(83,951)	32,359,625	83,951	—	—	—	—	—	83,951
Issuance of convertible preferred shares, net of issuance costs	—	—	9,221,888	50,118	—	—	—	—	—	50,118
Share-based compensation expense	—	—	—	—	—	—	1,019	—	—	1,019
Ordinary shares committed to be issued as part of license agreements	—	—	—	—	—	—	1,534	—	—	1,534
Ordinary shares issued as part of license agreements	—	—	—	—	1,849,545	—	1,653	—	—	1,653
Foreign currency translation adjustment	—	—	—	—	—	—	—	4,398	—	4,398
Net loss	—	—	—	—	—	—	—	—	(39,744)	(39,744)
Balance at December 31, 2017	**—**	**$ —**	**41,581,513**	**$ 134,069**	**11,154,720**	**$ —**	**$ 7,610**	**$ 4,127**	**$ (59,401)**	**$ 86,405**

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited
Consolidated statements of cash flows
(In thousands, except share amounts)

	Year ended December 31,	
	2016	**2017**
Cash flows from operating activities		
Net loss	$ (19,085)	$ (39,744)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	6	302
Share-based compensation	204	1,019
Non-cash consideration for licenses	3,089	3,126
Change in fair value of tranche obligation liability	(289)	—
Changes in components of operating assets and liabilities:		
Other receivables	—	(1,168)
Prepaid and other assets	(639)	(2,737)
Accounts payable	666	1,930
Accrued expenses and other current liabilities	1,460	4,672
Other long-term liabilities	22	113
Net cash used in operating activities	(14,566)	(32,487)
Cash flows from investing activities		
Purchases of property and equipment	(190)	(1,559)
Net cash used in investing activities	(190)	(1,559)
Cash flows from financing activities		
Proceeds from the issuance of convertible preferred shares, net of issuance costs	18,034	115,696
Net cash provided by financing activities	18,034	115,696
Effect of exchange rate changes on cash	(751)	4,709
Net increase in cash	2,527	86,359
Cash—beginning of year	970	3,497
Cash—end of year	$ 3,497	$ 89,856
Supplemental disclosure of non-cash investing and financing activities		
Conversion of promissory note to convertible preferred shares	$ 946	$ —
Issuance of tranche obligations with convertible preferred shares	2,459	—
Settlement of tranche obligations	451	1,402
Property and equipment included in accrued expenses and accounts payable at period end	$ —	$ 1,247

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited

Notes to consolidated financial statements

Years ended December 31, 2016 and 2017
(amounts in thousands, except share and per share data)

1. Nature of business and basis of presentation

Orchard Therapeutics Limited (the "Company"), a limited company incorporated pursuant to the laws of England and Wales in September 2015, is a commercial-stage fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. The Company's gene therapy approach seeks to transform a patient's own, or autologous, hematopoietic stem cells (HSCs) into a gene-modified drug product to treat the patient's disease through a single administration.

The Company has acquired and developed a portfolio of autologous *ex vivo* gene therapies focused on three franchises in which it accumulates expertise, including primary immune deficiencies, inherited metabolic disorders and hemoglobinopathies. The Company's programs include Strimvelis, the first autologous *ex vivo* gene therapy approved by the EMA for ADA-SCID, three clinical programs in advanced registrational studies in metachromatic leukodystrophy ("MLD"), Wiskott–Aldrich syndrome ("WAS") and adenosine deaminase severe combined immunodeficiency ("ADA-SCID"), other clinical programs in X-linked chronic granulomatous disease ("X-CGD") and transfusion-dependent beta-thalassemia ("TDBT"), as well as an extensive preclinical pipeline.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's technology will be obtained, that any products developed will obtain necessary government regulatory approval or that any products, if approved, will be commercially viable. The Company operates in an environment of rapid technological innovation and substantial competition from pharmaceutical and biotechnological companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Through December 31, 2017, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares. The Company has incurred recurring losses since its inception, including net losses of $19.1 million and $39.7 million for the years ended December 31, 2016 and 2017, respectively. As of December 31, 2017, the Company had an accumulated deficit of $59.4 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expected that its cash on hand as of December 31, 2017 of $89.9 million, together with the approximately $150.0 of gross cash proceeds received from the Company's sale of Series C convertible preferred shares in August 2018 (Note 14) will be sufficient to fund its operations and capital expenditure requirements through at least 12 months from the issuance date of these consolidated financial statements.

The Company is seeking to complete an initial public offering ("IPO") of American Depositary Shares ("ADSs") each representing an ordinary share of the Company. In the event the Company

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

does not complete an IPO, the Company expects to seek additional funding through private equity financings, debt financings, or other capital sources, including collaborations with other companies, government contracts or other strategic transactions. The Company may not be able to obtain funding on acceptable terms, or at all, because the terms of any financing may adversely affect the holdings or the rights of the Company's shareholders.

If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company and its wholly owned subsidiary, Orchard Therapeutics North America, after elimination of all intercompany accounts and transactions.

2. Summary of significant accounting policies

Use of estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the fair values of ordinary and convertible preferred shares, the fair value of tranche obligations, share-based compensation and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Unaudited pro forma information

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma information represents information for Orchard Therapeutics plc for the years ended December 31, 2016 and 2017.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Unaudited supplemental pro forma information

In the accompanying consolidated statements of operations and comprehensive loss, the unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2017 has been prepared to give effect to, upon closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2017 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

Concentration of credit risk

The Company has no significant off-balance sheet risk, such as foreign currency contracts, options contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and other receivables. Periodically, the Company maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

Foreign currency translation

The Company maintains its consolidated financial statements in its functional currency, pounds sterling. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency at exchange rates prevailing at the balance sheet date. Non-monetary assets and liabilities denominated in foreign currencies are translated into the functional currency at the exchange rates prevailing at the date of the transaction. Exchange gains or losses arising from foreign currency transactions are included in the determination of net income (loss) for the respective periods. The Company recorded foreign currency loss of $0.2 million and $1.2 million for the years ended December 31, 2016 and 2017, respectively, which is included in other expense in the statements of operations and comprehensive loss.

For financial reporting purposes, the consolidated financial statements of the Company have been translated into United States dollars. Assets and liabilities have been translated at the exchange rates prevailing at the balance sheet date, while revenue and expenses are translated at the average exchange rates over the reporting period. Shareholders' equity amounts are translated based on historical exchange rates as of the date of each transaction. Translation adjustments are not included in determining net income (loss) but are included in foreign currency translation adjustment to other comprehensive loss, a component of shareholders' (deficit) equity.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Cash and cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at acquisition to be cash equivalents. In 2016 and 2017, the Company did not have any cash equivalents.

Property and equipment

Property and equipment are recorded at cost and depreciated or amortized using the straight-line method over the following estimated useful lives.

Property and equipment:	Estimated useful life
Lab equipment	5-10 years
Leasehold improvements	Shorter of lease term or estimated useful life
Furniture and fixtures	4 years
Office and computer equipment	3-5 years

As of December 31, 2016 and 2017, the Company's property and equipment consisted of furniture and fixtures, office and computer equipment, lab equipment and leasehold improvements. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is included in the statement of operations and other comprehensive loss. Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, as determined in accordance with the related accounting literature. To date, the Company has not recorded any impairment losses on long-lived assets.

Fair value measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

(an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying values of the Company's other receivable, accounts payable, accrued expenses and other current liabilities approximate their fair values due to the short-term nature of these assets and liabilities.

Tranche obligations

In 2016, Series A convertible preferred shares (the "Series A convertible preferred shares") were issued in three tranches. The Company was obligated to issue second and third tranches of Series A convertible preferred shares once certain business milestones were met; these tranches were recognized as tranche obligations, which are subject to revaluation at each balance sheet date. Changes in fair value were recorded as a component of other income (expense) until the settlement of the tranche obligation.

The fair values of the tranche obligations are based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The tranche obligations are valued as a forward contract, and the values are determined using a probability-weighted present value calculation. In determining the fair values of the tranche obligations, estimates and assumptions impacting fair value included the fair value of the Company's convertible preferred shares, risk-free interest rates, the probability and estimated timing of the tranche closings, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares. The Company determines the per share fair value of the underlying convertible preferred shares using the option pricing model ("OPM"), which considers the preferred share price paid by

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Notes to consolidated financial statements (continued)

investors, the time to liquidity and volatility. In the OPM, the timing of the liquidity event determines the assumed life in the Black-Scholes calculation. The Company estimates a time to liquidity taking into account the future tranche funding. If the future tranche is not expected to be funded, a liquidity event will be assumed to have occurred. If the tranche is expected to be funded, a longer-term liquidity event is assumed to have occurred. Volatility is estimated based on the daily trading histories of comparable public companies. The risk-free interest rate is determined by reference to the United States Treasury yield curve. The Company estimated a 0% dividend yield based on the expected dividend yield and the fact that it has never paid or declared dividend.

Segment information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision maker in deciding how to allocate resources and assess performance. The Company and the Company's chief operating decision maker, the Company's Chief Executive Officer, views the Company's operations and manages its business as a single operating segment, which is focused on discovering, acquiring, developing and commercializing gene therapies for patients with rare disorders. The Company operates in two geographic regions: the United Kingdom and United States. The Company had fixed assets of $0.5 million and $2.2 million located in the United Kingdom and United States, respectively, as of December 31, 2017.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, facilities costs, depreciation, third-party license fees, and external costs of outside vendors engaged to conduct clinical development activities and clinical trials, as well as to manufacture clinical trial materials. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are recorded as prepaid expenses. Such amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered.

Research contract costs and accruals

The Company has entered into various research and development-related contracts. These agreements are cancelable, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

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Notes to consolidated financial statements (continued)

Share-based compensation

The Company measures share-based awards granted to employees and directors based on the fair value on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, the Company issues share-based awards with only service-based vesting conditions and records the expense for these awards using the straight-line method. The Company has not issued any share-based awards with performance-based vesting conditions.

Prior to the adoption of Accounting Standards Update ("ASU") No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* ("ASU 2018-07"), which is discussed below under "Recently adopted accounting pronouncements," the measurement date for non-employee awards was generally the date the services were completed, resulting in financial reporting period adjustments to share-based compensation during the vesting terms for changes in the fair value of the awards. At the end of each financial reporting period prior to completion of the service period, the fair value of the unvested awards was remeasured using the then-current fair value of the Company's ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model.

After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of the grant. The compensation expense for non-employees is recognized, without changes in the fair value of the award, over the requisite service period, which is the vesting period of the respective award.

The Company classifies share-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

The fair value of each option is estimated on the date of grant using the Black-Scholes option pricing model. Given the absence of an active market for the Company's ordinary shares, the board of directors, the members of which the Company believes have extensive business, finance, and venture capital experience, was required to estimate the fair value of the Company's ordinary share at the time of each grant of a share-based award. The board of directors determined the estimated fair value of the Company's equity instruments based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector. The Company and the board of directors utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants' Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require the Company's judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of the Company's ordinary shares at each grant date, including the following factors: (1) prices paid for the Company's convertible preferred shares, which the Company had sold to outside investors in arm's-length transactions, and the rights, preferences, and privileges of the Company's convertible preferred shares and ordinary shares; (2) valuations performed by an independent valuation specialist; (3) the Company's stage of development; (4) the fact that the grants of share-based awards involved illiquid securities in a private company; and (5) the likelihood of

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Notes to consolidated financial statements (continued)

achieving a liquidity event for the ordinary shares underlying the share-based awards, such as an IPO or sale of the Company, given prevailing market conditions.

Ordinary share valuations were prepared using the OPM to estimate the Company's enterprise value. The OPM treats ordinary and convertible preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the ordinary shares have value only if the funds available for distribution to shareholders exceeded the value of the convertible preferred shares liquidation preferences at the time of the liquidity event, such as a strategic sale or a merger. A discount for lack of marketability of the ordinary shares is then applied to arrive at an indication of value for the ordinary shares. The hybrid method is a probability weighted expected return method, PWERM, where the equity value in one or more scenarios is calculated using an OPM. The PWERM is a scenario-based methodology that estimates the fair value of ordinary shares based upon an analysis of future values for the company, assuming various outcomes. The ordinary shares' value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each share class. The future value of the ordinary shares under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the ordinary shares.

The Company estimates its expected share price volatility based on the historical volatility of publicly traded peer companies and expects to continue to do so until it has adequate historical data regarding the volatility of its own traded share price.

The expected term of the Company's share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the United States Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the Company's history of not paying cash dividends on ordinary shares. The Company does not expect to pay any cash dividends in the foreseeable future.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' equity (deficit) that result from transactions and economic events other than those with shareholders. For the years ended December 31, 2016 and 2017, comprehensive (loss) income included a loss of $0.3 million and a gain of $4.4 million, respectively, related to foreign currency translation adjustments.

Income tax credit

As a company that carries out extensive research and development activities, the Company seeks to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program ("SME Program") and the Research and Development Expenditure program ("RDEC Program"). Qualifying expenditures largely comprise

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income. Such credits are accounted as reductions in research and development expense in the period in which the expenditures were incurred.

Based on criteria established by HM Revenue and Customs ("HMRC"), management of the Company expects a proportion of expenditures being carried in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the RDEC Program for the years ended December 31, 2016 and 2017. The Company will assess whether it is possible to qualify under the more favorable SME regime for future accounting periods, but this may be affected as a result of becoming a United States public company.

The RDEC credits are not dependent on the Company generating future taxable income or on the ongoing tax status or tax position of the Company. As such the Company has recorded United Kingdom research and development tax credit as an offset to research and development expense in the consolidated statements of operations and comprehensive loss of $0.2 million and $0.7 million for the years ended December 31, 2016 and 2017, respectively. As of December 31, 2016, and 2017, the Company's tax incentive receivable from the United Kingdom government was $0.1 million and $0.9 million, respectively. These amounts have not yet been paid to the Company by HMRC.

Income taxes

The Company is subject to United Kingdom corporate taxation. Due to the nature of its business, the Company has generated losses since inception and has therefore not paid United Kingdom corporation tax. The Company's income tax credit recognized represents the sum of the research and development tax credits recoverable in the United Kingdom and income tax payable in the United States.

Unsurrendered United Kingdom losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of United Kingdom taxable profits.

Value Added Tax ("VAT"), is broadly charged on all taxable supplies of goods and services by VAT-registered businesses. Under current rates, an amount of 20% of the value, as determined for VAT purposes, of the goods or services supplied is added to all sales invoices and is payable to HMRC. Similarly, VAT paid on purchase invoices is generally reclaimable from HMRC.

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood

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Notes to consolidated financial statements (continued)

that its deferred tax assets will be recovered in the future and, to the extent the Company believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company is subject to corporation taxes in the United Kingdom and the United States. The calculation of the Company's tax provision involves the application of both United Kingdom or United States tax law and requires judgement and estimates.

The Company accounts for uncertainty in income taxes by recognizing in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed as the amount of benefit to recognize in the consolidated financial statements. The amount of benefits that may be used is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate, as well as the related net interest and penalties.

Net income (loss) per share

The Company follows the two-class method when computing net income (loss) per share as the Company has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of ordinary and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to ordinary shareholders for the period to be allocated between ordinary and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to ordinary shareholders is computed by dividing the net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period. Diluted net income (loss) attributable to ordinary shareholders is computed by adjusting net income (loss) attributable to ordinary shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to ordinary shareholders is computed by dividing the diluted net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares. For purpose of this calculation, outstanding options and convertible preferred shares are considered potential dilutive ordinary shares.

The Company's convertible preferred shares contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss attributable to ordinary shareholders, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to ordinary

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Notes to consolidated financial statements (continued)

shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive. The Company reported a net loss attributable to ordinary shareholders for the years ended December 31, 2016 and 2017.

Recently adopted accounting pronouncements

In June 2018, the Financial Accounting Standards Board ("FASB") issued ASU No. 2018-07 ("ASU 2018-07"). ASU 2018-07 expands the scope of Topic 718, *Compensation—Stock Compensation*, to include share-based payments issued to nonemployees for goods or services. Consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. ASU 2018-07 supersedes Subtopic 505-50, *Equity—Equity-Based Payments to Non-Employees*. The amendments are effective for public companies for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. For all other companies, the amendments are effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted, but no earlier than a company's adoption date of Topic 606. ASU 2018-07 was adopted as of January 1, 2017 and did not have a material impact on the Company's financial position, results of operations or cash flows. The adoption will impact the value at which share-based payments to nonemployees is recognized.

In January 2017, the FASB issued ASU No. 2017-01*, Business Combinations (Topic 805) Clarifying the Definition of a Business* ("ASU 2017-01"). ASU 2017-01 clarifies the definition of a business by adding guidance to assist entities in evaluating whether transactions should be accounted for as acquisitions of assets or businesses. The definition of a business affects many areas of accounting including acquisitions, disposals, goodwill and consolidation. The ASU is effective for public entities for fiscal years beginning after December 15, 2017. For all other entities, the guidance is effective for annual periods beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early application is permitted for transactions for which the acquisition date occurs before the effective date when the transaction has not been reported in financial statements that have been issued or made available for issuance. As such, the Company adopted this standard effective as of January 1, 2016 and applied it to its arrangements entered into during the years ended December 31, 2016 and 2017 (Note 8).

In March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* ("ASU 2016-09"). ASU 2016-09 addresses several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross share compensation expense with actual forfeitures recognized as they occur, and classification on the statement of cash flows. Certain of these changes are required to be applied retrospectively, while other changes are required to be applied prospectively. ASU 2016-09 is effective for public entities for annual periods beginning after December 15, 2016, and interim periods within those annual periods. For all other entities, the guidance is effective for annual periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2018. Early adoption is permitted for any entity in any interim or

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Notes to consolidated financial statements (continued)

annual period and an entity that elects early adoption must adopt all of the amendments in the same period. The Company early adopted ASU 2016-09 effective as of January 1, 2016. The adoption of ASU 2016-09 did not have a material impact on the Company's financial position, results of operations or cash flows.

In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes* ("ASU 2015-17"), which requires deferred tax liabilities and assets to be classified as non-current in the consolidated balance sheet. ASU 2015-17 is effective for public entities for annual periods beginning after December 15, 2016, and interim periods within those annual periods. For all other entities, the guidance is effective for annual periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2018. Early adoption is permitted and the Company elected to early adopt the standard on January 1, 2016. The adoption of ASU 2015-17 had no material impact on the Company's financial position, results of operations or cash flows.

In November 2014, the FASB issued ASU No. 2014-16, *Determining Whether the Host Contract in a Hybrid Financial Instrument Issued in the Form of a Share Is More Akin to Debt or to Equity* ("ASU 2014-16"). The guidance requires an entity to determine the nature of the host contract by considering all stated and implied substantive terms and features of the hybrid financial instrument, weighing each term and feature on the basis of the relevant facts and circumstances (commonly referred to as the whole-instrument approach). The Company adopted the standard modified retrospectively to all periods presented on the required effective date of January 1, 2016, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In August 2014, the FASB issued ASU No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* ("ASU 2014-15"). The amendments in this update explicitly require a company's management to assess an entity's ability to continue as a going concern and to provide related footnote disclosures in certain circumstances. The new standard is effective for all entities for annual periods ending after December 15, 2016 and for annual and interim periods thereafter. Early adoption is permitted. The Company adopted ASU 2014-15 as of the required effective date of December 31, 2016. This guidance relates to footnote disclosure only, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* ("ASU 2014-09"), which supersedes existing revenue recognition guidance under GAAP. The standard's core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods or services. The standard defines a five-step process to achieve this principle and will require companies to use more judgment and make more estimates than under the current guidance. The Company expects that these judgments and estimates will include identifying performance obligations in the customer contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and

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Notes to consolidated financial statements (continued)

cash flows arising from customer contracts. In August 2015, the FASB issued ASU 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date,* which delays the effective date of ASU 2014-09 such that the standard is effective for public entities for annual period beginning after December 15, 2017, including interim periods within those fiscal years. For all other entities, the guidance is effective beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early adoption of the standard is permitted for annual periods beginning after December 15, 2016, including interim periods within those fiscal years. The Company adopted these revenue standards on January 1, 2017. In 2016 and 2017, the Company did not have any revenue.

Recently issued accounting pronouncements

In March 2018, the FASB issued ASU No. 2018-05, *Income Taxes (Topic 740): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 118* ("ASU 2018-05"). ASU 2018-05 amends SEC paragraphs in ASC 740 to reflect SEC Staff Accounting Bulletin (SAB) No.118. When the 2017 Tax Cuts and Jobs Act (the "Act") was signed into law, the SEC staff released SAB 118 for applying Topic 740 as it relates to the Act. SAB 118 outlines the approach companies may take if they determine that the necessary information is not available (in reasonable detail) to evaluate, compute, and prepare accounting entries to recognize the effect(s) of the Act by the time the financial statements are required to be filed. Companies may use this approach when the timely determination of some or all of the income tax effect(s) from the Act is incomplete by the due date of the financial statements. SAB 118 also prescribes disclosures that reporting entities must provide in these circumstances. The amendments to the Accounting Standards Codification became effective upon issuance. The Company has conducted a preliminary assessment of its income tax effects of the Act. Additional analysis of the law and the impact to the Company may be performed, if needed, and any impact will be finalized no later than the fourth quarter of 2018.

In July 2017, the FASB issued ASU No. 2017-11, *Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480), Derivatives and Hedging (Topic 815) (Part I) Accounting for Certain Financial Instruments with Down Round Features, (Part II) Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception* ("ASU 2017-11"). Part I applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred stock that contain down-round features. Part II replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. ASU 2017-11 is required to be adopted for public entities for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2018. For all other entities, the guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted for all entities. The Company is currently evaluating the impact that the adoption of ASU 2017-11 will have on its consolidated financial statements.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting* ("ASU 2017-09"), which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. Under the new guidance, modification accounting is required only if the fair value, the vesting conditions or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. ASU 2017-09 is effective for all entities annual periods, and interim periods within those annual periods, beginning after December 15, 2017. Early adoption is permitted, including adoption in any interim period, for 1) public business entities for reporting periods for which financial statements have not yet been issued and 2) all other entities for reporting periods for which financial statements have not yet been made available for issuance. The Company will adopt ASU 2017-09 as of the required effective date of January 1, 2018. The adoption of ASU 2017-09 is expected to have an impact on the modification of share-based awards, if any, after the date of adoption. The adoption of ASU 2017-09 is not expected to have a material impact on the Company's financial position, results of operations or cash flows.

In February 2016, the FASB issued ASU No. 2016-02*, Leases (Topic 842)* ("ASU 2016-02"), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases today. In January 2018, the FASB issued ASU 2018-01, *Leases (Topic 842)*, ("ASU 2018-01"), which adds two practical expedients to the new lease guidance. Topic 842 is effective for annual periods beginning after December 15, 2018, including interim periods within those fiscal years for public business entities, certain not-for-profit, and employee benefit plans that file with the SEC. For all other entities, the guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted for all entities. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

3. Fair value of financial assets and liabilities

The Company had no financial assets measured at fair value on a recurring basis at December 31, 2016 or 2017.

The following table presents information about the Company's financial liabilities that have been measured at fair value on a recurring basis as of December 31, 2016 (there were no financial liabilities measured at fair value on a recurring basis as of December 31, 2017):

	Fair value measurements as of December 31, 2016 using:			
	Level 1	Level 2	Level 3	Total
				(in thousands)
Liabilities:				
Tranche obligations	$ —	$ —	$ 1,402	$1,402
	$ —	$ —	$ 1,402	$1,402

The tranche obligations in the table above represents the Company's obligation to issue for sale Series A convertible preferred shares once certain business milestones were met. The fair value of the tranche obligations was based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The tranche obligations are valued as a forward contract as described in Note 2. The Company assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. The Company recognized changes in fair value of these tranche obligations as a component of other income (expense) in its consolidated statement of operations and comprehensive loss.

Estimates and assumptions impacting the fair value measurement included the fair value of the Company's convertible preferred shares, risk-free interest rate, the probability and estimated timing of each tranche closings, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares (Note 2). Significant changes to the fair value of the underlying shares would have resulted in a significant change in the fair value measurements.

The tranche obligations were settled when the respective second and third tranches of Series A convertible preferred shares were issued in July 2016 and January 2017.

The following assumptions were used in valuing the tranche obligations:

	Year Ended December 31, 2016
Risk-free interest rate	0.00 - 0.53%
Expected dividend yield	0.00%
Expected term (in years)	0.00 - 0.92
Expected volatility	75.5 - 89.9%
Fair value of convertible preferred shares	$ 1.00 - $1.58

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following table provides a rollforward of the fair value of the tranche obligations measured at fair value on a recurring basis using Level 3 significant unobservable inputs:

	Tranche obligations
	(in thousands)
Balance at December 31, 2015	$ —
Issuance of tranche obligations to purchase convertible preferred shares	2,459
Change in fair value of second tranche obligation	(424)
Settlement of second tranche obligation upon issuance of convertible preferred shares	(451)
Change in fair value of third tranche obligation	135
Effect of exchange rate changes on tranche obligation	(317)
Balance at December 31, 2016	1,402
Settlement of third tranche obligation upon issuance of convertible preferred shares	(1,402)
Balance at December 31, 2017	$ —

4. Property and equipment

Property and equipment consist of the following:

	December 31,	
	2016	2017
	(in thousands)	
Property and equipment:		
Lab equipment	$178	$ 2,708
Leasehold improvements	—	244
Furniture and fixtures	12	59
Office and IT equipment	—	12
Property and equipment	190	3,023
Less: accumulated depreciation	(6)	(310)
Property and equipment, net	$184	$ 2,713

Depreciation expense for the years ended December 31, 2016 and 2017 was $6,000 and $0.3 million, respectively.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

5. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2016	2017
	(in thousands)	
Accrued external research and development expenses	$1,260	$1,834
Accrued payroll and related expenses	244	2,090
Accrued professional fees	126	394
Accrued other	85	279
Deferred UCLA reimbursement	—	2,267
Total accrued expenses and other current liabilities	$1,715	$6,864

As of December 31, 2016, the Company did not have property and equipment that was received but not yet invoiced. As of December 31, 2017, accrued other includes $0.1 million of lab equipment that was acquired and received but not yet invoiced.

6. Shareholders' equity and convertible preferred shares

Convertible preferred shares

As of December 31, 2016, the Company's Articles of Association (the "Articles") authorized a total of 21,000,000 convertible preferred shares with a par value of £0.00001 per share, all of which have been designated as Series A convertible preferred shares. As of December 31, 2017, the Articles, as further amended and restated (the "Amended Articles"), authorized a total of 42,198,154 convertible preferred shares with a par value of £0.00001 per share, of which 21,000,000 shares have been designated as Series A convertible preferred shares and 21,198,154 shares have been designated as Series B convertible preferred shares (the "Series B convertible preferred shares").

Until September 2017, the Series A and Series B convertible preferred shares (collectively, the "Convertible Preferred Shares") were classified in temporary equity as the Convertible Preferred Shares were contingently redeemable. A contingent redemption feature, which is at the option of the Company, could have been exercised by a holder of the Convertible Preferred Shares while that holder controlled a majority of the Company's board of directors. The Convertible Preferred Shares did not become redeemable as the contingency had not been met or determined to be probable.

In September 2017, the Company's board of directors was expanded so that the holder of the Convertible Preferred Shares no longer controlled the Company's board of directors through a majority of seats. Based on this change, the redemption feature from September 2017 onward is exercisable only in an event that is within the control of the Company. At that date, the Convertible Preferred Shares were reclassified to permanent equity within shareholders' equity on the Company's consolidated balance sheets.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

In December 2015, the Company issued unsecured convertible loan notes ("the Notes") to an investor for principal amount of $0.9 million. The first six months from date of the Note issuance were interest free. After six months, an interest rate of 3% per annum was charged and shall accrue monthly in arrears. In February 2016, as part of the issuance of the first tranche of Series A convertible preferred shares, the Notes of $0.9 million were converted into 654,000 Series A convertible preferred shares at conversion price of £1.00.

Preferred share financings

In February 2016, the Company issued 6,666,667 Series A convertible preferred shares at a price of £1.00 per share (the "Series A Original Issue Price") of which 6,012,667 Series A convertible preferred shares were issued for net proceeds of $8.5 million and 654,000 Series A convertible preferred shares were issued in settlement of the Notes.

In May 2016, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of $0.4 million.

In July 2016, the Company issued and sold 6,666,667 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of $8.7 million.

In August 2016, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of $0.4 million.

In January 2017, the Company issued and sold 6,666,667 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of $8.2 million.

In February 2017, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of $0.4 million.

In March 2017, the Company issued and sold 7,254,000 Series B convertible preferred shares at a price of £4.019 per share (the "Series B Original Issue Price") for net proceeds of $36.0 million.

In August 2017, the Company issued and sold 4,105,625 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of $21.0 million.

In October 2017, the Company issued and sold 5,817,801 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of $30.8 million.

In December 2017, the Company issued and sold 3,404,087 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of $18.3 million.

In December 2017, the Company received proceeds of $1.0 million for 188,313 Series B convertible preferred shares, which were subsequently issued in January 2018 (Note 14).

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

As of each balance sheet, the Convertible Preferred Shares consisted of the following:

	December 31, 2016 (in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	14,000,000	$ 16,970	$ 17,222	14,000,000
	21,000,000	14,000,000	$ 16,970	$ 17,222	14,000,000

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2016.

	December 31, 2017 (in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	$ 26,994	$ 28,337	21,000,000
Series B convertible preferred shares	21,198,154	20,581,513	107,075	111,617	20,581,513
	42,198,154	41,581,513	$134,069	$ 139,954	41,581,513

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2017.

The holders of the Convertible Preferred Shares have the following rights and preferences as of December 31, 2017:

Voting

Each Series A and Series B share shall confer one right to vote at all general meetings and to receive and vote on proposed written resolutions of the Company.

Conversion

Each Series A preferred share shall be convertible, at the option of the holder, at any time and from time to time, and without the payment of additional consideration, into an ordinary share as is determined by dividing the applicable Series A Original Issue Price by the Series A Conversion Price. Each Series B preferred share shall be convertible, at the option of the holder, at any time and from time to time, and without the payment of additional consideration, into an ordinary share as is determined by dividing the applicable Series B Original Issue Price by the Series B Conversion Price.

The Series A Conversion Prices were equal to each applicable Series A Original Issue Price as noted above. The Series B Conversion Prices were equal to each applicable Series B Original Issue Price as noted above. As of December 31, 2016 and 2017, each Preferred Share was convertible into one ordinary share.

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Notes to consolidated financial statements (continued)

As set forth in the Amended Articles, the Series A and B Conversion Prices shall be adjusted when there is a deemed issuance of additional convertible preferred shares issued at a price lower than Series A and Series B Original Issue Prices or issuance of an instrument with rights that could dilute the interest of Series A and B holders. In addition, each Preferred Share will be automatically converted into an ordinary share at the applicable conversion ratio then in effect for each series of Convertible Preferred Shares upon the earlier of (i) the closing of a firm commitment underwritten public offering of its ordinary shares with gross proceeds to the Company of at least $50.0 million and at a price per share of not less than £4.8228, subject to appropriate adjustment in the event of any share split, share dividend, combination or other similar recapitalization, or (ii) a date specified vote or written consent of the holders of a majority of Convertible Preferred Shares, voting together as a single class on an as-if-converted to ordinary shares basis.

Dividends

The holders of the Series A convertible preferred shares, Series B convertible preferred shares, and ordinary shares are entitled to receive non-cumulative dividends, if and when declared by the Company's board of directors, subject to shareholder consent. The Series A convertible preferred shares, Series B convertible preferred shares and ordinary shares rank equally in all respects (on an as converted basis) for the purpose of any dividend that is declared or paid. On a distribution of assets on a liquidation, share sale, asset sale or IPO, the holders of Series A convertible preferred shares, and Series B convertible preferred shares are entitled to receive any declared but unpaid dividend, in the order of the priority set out in Liquidation Preference below, on each outstanding Series A convertible preferred share and Series B convertible preferred share. No dividends were declared or paid during the years ended December 31, 2016 or 2017.

Liquidation preference

In the event of a distribution of assets on liquidation or a return of capital (other than a conversion, redemption or purchase of shares), the surplus remaining after settling the Company's assets and liabilities will be distributed to the individuals holding ordinary shares, Series A and Series B convertible preferred shares on a pro rata basis (as if the ordinary shares and the Convertible Preferred Shares constituted one class) as described in the Amended Articles, except if the per share amount for Series A and Series B convertible preferred shares results in a price per share less than its original issue price. If the price per share is less than the original issue price for preferred shareholders, the shareholders will be paid an amount equal to the subscription price and the remainder of the assets will be distributed on a pro rata basis to the remaining ordinary shareholders.

Redemption

The Amended Articles do not provide redemption rights to the holders of Convertible Preferred Shares.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Ordinary shares

The voting, dividend and liquidation rights of the holders of the Company's ordinary shares are subject to and qualified by the rights, powers and preferences of the holders of the Convertible Preferred Shares set forth above. Each ordinary share entitles the holder to one vote, together with the holders of Convertible Preferred Shares, on all matters submitted to the shareholders for a vote. The holders of Convertible Preferred Shares are entitled to elect a total of three directors of the Company. The holders of ordinary shares are entitled to elect the remaining directors of the Company by vote of a majority of such shares. Ordinary shareholders are entitled to receive dividends, as may be declared by the board of directors, if any, subject to the Liquidation Preference priority noted above. Through December 31, 2017, no cash dividends have been declared or paid.

As of December 31, 2016, and 2017, the Company had authority to allot ordinary shares up to a maximum nominal value of £675,000 and £675,413, respectively, with a normal value of £0.00001 per share. The authority has taken into consideration the conversion of outstanding Convertible Preferred Shares of 14,000,000 and 41,581,513 as of December 31, 2016 and 2017, respectively; 1,113,000 and 625,511 ordinary shares the Company committed to issue as part of its license and research agreements as of December 31, 2016 and 2017, respectively; 2,260,966 and 5,223,443 for the exercise of outstanding share options, as of December 31, 2016 and 2017, respectively; and 5,904,618 and 2,942,141 shares remaining available for future issuance under the 2016 Share Option Plan as of December 31, 2016 and 2017, respectively.

Ordinary share issuances

In February 2016, and amended in July 2017, the Company entered into a license agreement (the "UCLB/UCLA License Agreement") with UCL Business PLC ("UCLB"), which is the commercialization company of University College London, and The Regents of the University of California ("UCLA") (Note 8), pursuant to which the Company issued 4,300,000 and 1,529,545 ordinary shares in 2016 and 2017, respectively, to UCLB. The shares were recorded at their fair values as of the time the agreement was executed or modified, which was an aggregate of $3.8 million. Amounts totaling $2.1 million and $1.7 million were recorded to research and development expense for the years ended December 31, 2016 and 2017, respectively.

In November 2016, the Company entered into a license and development agreement with Oxford BioMedica U.K. Limited ("Oxford BioMedica") (Note 8). As consideration for the rights and licenses granted to Orchard under the license and development agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica in December 2016. The Company also agreed to grant additional ordinary shares upon achievement of specified milestones. In November 2017, the first milestone was achieved and the Company was obligated to issue an additional 188,462 shares. The shares issued in 2016 and 2017 were recorded based on their fair values as of the time the agreement was executed of $0.5 million and $0.1 million, respectively. The amounts were recorded to research and development expense in the years ended December 31, 2016 and 2017, respectively.

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

its programs. As part of the consideration related to these license agreement, the total share commitment was 1,288,000 and 469,049 ordinary shares in 2016 and 2017, respectively. Pursuant to these agreements, the Company issued 1,000,000 and 320,000 ordinary shares in 2016 and 2017, respectively. The share commitments were recorded to research and development expense based on their fair values as of the time the respective agreement was executed or modified. The amounts were $0.5 million and $1.4 million in 2016 and 2017, respectively.

As of December 31, 2016 and 2017, the Company had outstanding 9,305,175 and 11,154,720 ordinary shares, respectively.

Deferred shares

Deferred shares are a unit of equity in the Company. All deferred shares can be repurchased at any time by the Company at a purchase price of £0.00001 per share. Deferred shares have no rights attached to them, are not convertible to any other class of shares and are not redeemable. The entire class of deferred shares is entitled to a total of £1.00 from the distribution of assets on a liquidation or return of capital event.

In 2016, the Company converted 100,000 ordinary shares of an investor to deferred shares. In March 2017, the Company repurchased 100,000 deferred shares at £0.00001 per share and simultaneously cancelled them.

As of December 31, 2016, the Company had 100,000 deferred shares outstanding. There were no deferred shares outstanding as of December 31, 2017.

7. Share-based compensation

2016 Share option plan

In September 2016, the Company adopted the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the “2016 Plan”). The 2016 Plan provides for the Company to grant incentive and non-qualified options to officers, directors, consultants, and advisors to purchase the Company’s ordinary shares.

The total number of ordinary shares that may be issued under the 2016 Plan was 8,165,584 shares as of December 31, 2017, of which 2,942,141 shares remained available for future grant.

The Company typically grants options to United States employees and non-employees at exercise prices deemed by the board of directors to be equal to the fair value of the ordinary share at the time of grant and grant options to United Kingdom employees at an exercise price equal to the par value of the ordinary shares of £0.00001. The vesting period is determined by the board of directors, which is generally four years. An option’s maximum term is ten years.

Shares that are expired, terminated, surrendered or canceled under the 2016 Plan without having been fully exercised will be available for future awards.

During the years ended December 31, 2016 and 2017, the Company granted options to purchase 1,507,763 and 3,039,235 ordinary shares, respectively, to employees and directors. The Company

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

recorded share-based compensation expense for options granted to employees and directors of $0.1 million and $0.9 million during the years ended December 31, 2016 and 2017, respectively.

In 2016, the Company granted options to purchase 753,203 ordinary shares to a non-employee. There were no options granted to non-employees during the year ended December 31, 2017. The Company recorded share-based compensation expense for options granted to the non-employee of $0.1 million and $0.2 million during the years ended December 31, 2016 and 2017, respectively.

Option valuation

When utilizing the Black-Scholes option-pricing model to determine the grant date fair value of share options granted to employees or the vesting or re-measurement date fair value for awards granted to non-employees in 2016, the Company used the following assumptions:

Employees and directors

	Year ended December 31,	
	2016	**2017**
Risk-free interest rate	1.52% - 2.20%	1.99% - 2.30%
Expected term (in years)	6.08	6.08
Expected volatility	77.80% - 78.50%	78.00% - 80.00%
Expected dividend rate	0.00%	0.00%

Non-employee

	Year ended December 31,	
	2016	**2017**
Risk-free interest rate	1.61% - 2.4%	1.52%
Expected term (in years)	9.75	6.08
Expected volatility	79.4% - 79.7%	77.80%
Expected dividend rate	0.00%	0.00%

Expected Term: The expected term for employees represents the period that the options granted are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term). The expected term is applied to the share option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. Prior to the adoption of ASU 2018-07, expected term for non-employee grants was the contractual term of the options. After the adoption of ASU 2018-07, the expected term of share options granted to non-employees is determined in the same manner as share options granted to employees.

Expected Volatility: The Company used an average historical stock price volatility of comparable public companies within the biotechnology and pharmaceutical industry that were deemed to be representative of future share price trends as the Company does not have any trading history for its ordinary shares.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Risk-Free Interest Rate: The Company based the risk-free interest rate over the expected term of the options based on the constant maturity rate of United States Treasury securities with similar maturities as of the date of the grant.

Expected Dividend Rate: The Company has not paid and does not anticipate paying any dividends in the near future. Therefore, the expected dividend yield was zero.

Fair value of underlying ordinary shares: The Company determined the fair value of the underlying ordinary shares based on input from management and approved by the board of directors, as described in Note 2.

Options

The following table summarizes option activity under the 2016 Plan since December 31, 2016:

	Shares	Weighted average exercise price	Weighted average remaining contractual life	Aggregate intrinsic value
		(in thousands, except share and per share amounts)		
Options outstanding at December 31, 2016	2,260,966	$ 0.10	9.75	$ 1,466
Granted	3,039,235	1.58		
Exercised	—	—		
Canceled	(76,758)	0.01	9.48	228
Options outstanding at December 31, 2017	5,223,443	0.96	9.28	10,483
Vested as of December 31, 2017	973,529	0.14	8.65	2,716

The weighted average exercise price of options granted to United Kingdom employees in 2017 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees 2017 was $1.95.

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares.

The weighted average grant date fair value of the options granted during the years ended December 31, 2016 and 2017, was $0.73 per share and $2.16 per share, respectively.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Share-based compensation

Share-based compensation expense was classified in the consolidated statements of operations and comprehensive loss as follows:

	Year ended December 31,	
	2016	2017
		(in thousands)
Research and development	$ 181	$ 615
General and administrative	23	404
Total	$ 204	$ 1,019

The Company had 4,249,914 unvested options outstanding as of December 31, 2017. As of December 31, 2017, there was $6.4 million of unrecognized compensation expense related to unvested options, that is expected to be recognized over a weighted average period of approximately 3.19 years.

8. License and research arrangements

UCLB/UCLA License Agreement

In February 2016, and amended in July 2017, the Company entered into the UCLB/UCLA License Agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of $0.8 million for the license to the joint UCLB/UCLA technology and $1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 5,829,545 ordinary shares to UCLB, of which 4,300,000 and 1,529,545 ordinary shares were issued in 2016 and 2017, respectively. The Company recorded research and development expense based on the fair value of the ordinary shares as of the time the agreement was executed or modified. The Company was also obligated to make an additional cash payment for clinical data. As of December 31, 2016, it had accrued $0.6 million relating to the payment for clinical data in accrued expenses and other current liabilities on the consolidated balance sheet. In 2017, the Company paid $0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

The Company recorded $4.6 million and $1.8 million of research and development costs, which comprise the upfront payments, issuance of ordinary shares and payments for clinical data, for the years ended December 31, 2016 and 2017, respectively.

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of $0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company is obligated to make payments to the parties of up to an

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

aggregate of $38.9 million upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

In connection with the UCLB/UCLA License Agreement, in February 2016 the Company sold an aggregate of 999,999 Series A convertible preferred shares at a price of £1.00 per share (Note 13).

Unless terminated earlier by either party, the UCLB/UCLA License Agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors for the Company (“Oxford BioMedica Agreement”). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved and the Company was committed to issue 188,462 ordinary shares in 2018. As of December 31, 2017, the Company’s remaining potential share obligation under the agreement comprised one milestone, which, upon achievement, would require the Company to issue additional ordinary shares.

The Company recorded $0.5 million to research and development expense upon execution of the Oxford BioMedica Agreement in 2016 and $0.1 million upon achievement of the first development milestone in 2017. The expense was determined based on the ordinary shares’ fair value as of the time the agreement was executed.

The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

Other license and research agreements

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. As part of the consideration related to these license agreement, the total share commitment was 1,288,000 and 469,049 ordinary shares and the Company made cash payments of $2.7 million and $0.4 million in 2016 and 2017, respectively. The Company recorded $3.2 million and $1.7 million to research and development expense in 2016 and 2017, respectively. In addition, the Company also committed to make certain clinical and regulatory milestone payments in the aggregate of $29.0 million as well as single-digit percentage royalties on net sales of products and services associated with the in-licensed technology.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

UCLA research agreement

In January 2017, the Company and UCLA executed a subcontract agreement ("UCLA Research Agreement"), whereby the Company would provide UCLA certain research and development services related to autologous lentiviral gene therapy in ADA-SCID as part of UCLA's existing ADA-SCID research program that is being funded by the California Institute for Regenerative Medicine ("CIRM"). The total reimbursement the Company may receive under the UCLA Research Agreement is $10.4 million, which may be received during the period from January 2017 to December 2021. The reimbursement is recognized as a reduction in research and development expense for research activities that have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM.

For the year ended December 31, 2017, the Company recorded $5.0 million as a reduction of research and development expenses related to the UCLA Research Agreement. As of December 31, 2017, the Company recorded $2.3 million within accrued expense and other liabilities on the Company's consolidated balance sheet related to the advance of reimbursements for research activities.

9. Income taxes

The provision for income taxes for the years ended December 31, 2016 and 2017 was computed at the United Kingdom statutory income tax rate. The income tax provision for the years then ended comprised:

	December 31,	
	2016	2017
	(in thousands)	
Current provision expense		
Federal—United States	$ —	$ —
State—United States	17	16
United Kingdom	—	—
Total current provision expense	17	16
Deferred provision expense		
Federal—United States	—	—
State—United States	3	37
United Kingdom	—	—
Total deferred provision expense	3	37
Total provision for income taxes	$ 20	$ 53

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Notes to consolidated financial statements (continued)

A reconciliation of income tax expense computed at the United Kingdom statutory income tax rate to income taxes as reflected in the consolidated financial statements is as follows:

	December 31,	
	2016	2017
	(in thousands)	
Income taxes at United Kingdom statutory rate	$(3,831)	$(7,640)
State income taxes	14	41
Permanent differences	75	115
Tax credits	(99)	(286)
Foreign rate differential	6	(40)
Change in valuation allowance	3,855	7,827
Impact of United States tax reform	—	36
Total provision expense for income taxes	$ 20	$ 53

Significant components of the Company's deferred tax assets and liabilities as of December 31, 2016 and 2017 consist of the following:

	December 31,	
	2016	2017
	(in thousands)	
Deferred tax assets		
Net operating loss carryforwards	$ 1,989	$ 9,483
Research and development credits	70	356
Share-based compensation	15	147
Amortization	1,457	2,156
Accruals	14	28
Total deferred tax assets	3,545	12,170
Valuation allowance	(3,503)	(11,882)
Net deferred tax assets	$ 42	$ 288
Deferred tax liabilities		
Depreciation	$ (44)	$ (328)
Other non-current liabilities (net deferred tax assets and liabilities)	$ (2)	$ (40)

As of December 31, 2016, the Company has approximately $9.9 million of United Kingdom net operating loss carryforwards with an indefinite life (but may be subject to certain utilization restrictions). Additionally, the Company has approximately $0.1 million of United States federal research and development credit carryforwards that begin to expire in 2036.

As of December 31, 2017, the Company has approximately $48.4 million of United Kingdom net operating loss carryforwards with an indefinite life (but may be subject to certain utilization restrictions). Additionally, the Company has approximately $0.8 million and $0.4 million of

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

United States federal net operating loss and federal research and development credit carryforwards that begin to expire in 2037 and 2036, respectively.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets, which primarily comprise net operating loss carryforwards and research and development credits. Management has considered the Company's history of cumulative net losses in the United States and United Kingdom, estimated future taxable income and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of its United States federal and United Kingdom deferred tax assets. Accordingly, a full valuation allowance has been established against these net deferred tax assets as of December 31, 2016 and 2017, respectively. The Company reevaluates the positive and negative evidence at each reporting period.

The Company files tax returns in the United Kingdom, United States and various U.S. states. With few exceptions, the Company is subject to United States federal, state and local, and foreign tax examinations by tax authorities from inception through present. As of December 31, 2017, the Company has recorded no liability for unrecognized tax benefits, interest, or penalties related to federal, state, and foreign income tax matters and there currently no pending tax examinations.

10. Net loss per share

The following table sets forth the computation of basic and diluted net loss per share:

	Year ended December 31	
	2016	2017
	(In thousands, except per share and share amounts)	
Net loss	$ (19,085)	$ (39,744)
Net loss attributable to ordinary shareholders	$ (19,085)	$ (39,744)
Weighted average ordinary shares outstanding, basic and diluted	8,872,333	11,086,808
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.15)	$ (3.58)

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all shares convertible into ordinary shares outstanding would have been anti-dilutive.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following securities are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

	December 31,	
	2016	2017
Convertible preferred shares	14,000,000	41,581,513
Share options	2,260,966	4,513,663
	16,260,966	46,095,176

In 2018, the Company issued 625,511 ordinary shares to third-party licensors. In January 2018, the Company issued an additional 616,641 Series B convertible preferred shares. In April 2018, the Company issued 15,563,230 Series B-2 convertible preferred shares as consideration for the GSK Agreement (as defined in Note 14). In August 2018, the Company issued 17,421,600 Series C convertible preferred shares (Note 14).

Unaudited pro forma net loss per share attributable to ordinary shareholders

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. The following represents pro forma earnings per share information for Orchard Therapeutics plc for the years ended December 31, 2016 and 2017:

	Year ended December 31	
	2016	2017
	(in thousands except per share and share amounts)	
Net loss attributable to ordinary shareholders	$ (19,085)	$ (39,744)
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	$ (2.69)	$ (4.48)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	7,100,528	8,872,768

Unaudited supplemental pro forma net loss per share attributable to ordinary shareholders

The unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2017 have been prepared to give effect to adjustments arising upon the closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2017 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

A reconciliation of the pro forma weighted-average number of ordinary shares used in computing supplemental pro forma basic and diluted net loss per share applicable to ordinary shareholders is as follows:

		Year ended December 31, 2017
		(in thousands except per share and share amounts)
Numerator:		
Net loss attributable to ordinary shareholders	$	(39,744)
Denominator		
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)		8,872,768
Pro forma adjustment to reflect assumed conversion of preferred share into ordinary share (unaudited)		23,183,438
Supplemental pro forma weighted average number of ordinary shares used in computing supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)		32,056,206
Supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	$	(1.24)

11. Commitments and contingencies

Lease agreements

In October 2016, the Company entered into a lease agreement for five years for laboratory space in Foster City, California, United States. The lease commencement date was October 1, 2016. The Company was provided with one month of free rent.

In January 2017, the Company entered into a lease agreement for office space in London, United Kingdom. The lease commenced on January 16, 2017 and expires on January 16, 2019.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Management has the option to terminate the lease at its discretion after at the end of the one-year anniversary of the lease.

In November 2017, the Company entered into a lease arrangement for laboratory space in Menlo Park, California, United States. The lease commenced on November 1, 2017 and expires on November 30, 2020. The Company was provided with one month of free rent.

The following table summarizes the future minimum lease payments due under operating leases as of December 31, 2017:

Due in:	(in thousands)
2018	$ 1,359
2019	1,029
2020	1,054
2021	191
Total	$ 3,633

In January 2018, the Company leased office space in London, United Kingdom. The lease has a term of five years and terminates in January 2023. The annual rental commitment approximates $0.8 million. In March 2018, the Company leased office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental commitment approximates $0.3 million.

The Company recognizes rent expense on a straight-line basis over the respective lease period and has recorded deferred rent for rent expense incurred but not yet paid.

The Company recorded rent expense of $0.2 million and $0.7 million for the years ended December 31, 2016 and 2017, respectively.

License agreements

The Company has entered into several license agreements (Note 8). In connection with these agreements the Company is required to make a number of milestone payments and annual license maintenance payments. The Company evaluated all milestone payments within the arrangements to estimate the probability of the Company meeting the milestones. The Company concluded in November 2017 a milestone relating to Oxford BioMedica Agreement was met (Note 8), and as a result, the associated milestone consideration of $0.1 million was recorded to research and development expense in the year ended December 31, 2017. The Company determined that no milestone payments were probable as of December 31, 2016.

Commitment with contract manufacturing organization

In 2017, Orchard entered into an agreement with a manufacturer of biotherapies in gene and cell therapies to purchase clinical material to be used in clinical trials. The Company has committed to place a minimum of three orders of clinical material over the next two years. The value of each order shall be determined by the specification and volume of the order placed. The Company expects to place two orders totaling $2.1 million in 2018 and one order of $1.1 million in 2019.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

12. Benefit plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to five percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid $31,000 and $0.2 million in matching contributions for the years ended December 31, 2016 and 2017, respectively.

13. Related-party transactions

UCLB

UCL Technology Fund LP ("UCLTF") is affiliated with UCLB. On February 6, 2016, UCLB through its associate UCLTF, entered into a Subscription and Shareholders' Agreement with the Company to purchase an aggregate of 999,999 Series A shares (Note 6). At the same time, UCLB also entered into the UCLB/UCLA License Agreement (Note 8), through which the Company was granted licenses to certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories. In 2016, the Company also agreed to sponsor a short-term research program with UCLB with total program costs of $0.5 million. In 2016 and 2017, the Company incurred $0.4 million and $0.2 million of consulting fees, with an affiliate of UCLB, respectively.

Other

In December 2017, the Company sold to its Chief Executive Officer, Chief Medical Officer and Senior Vice President of Business Development and Alliance Management 49,763, 12,440 and 4,976 Series B convertible preferred shares at a price of £4.019 per share for proceeds of $0.3 million, $67,000 and $27,000, respectively.

14. Subsequent events

For its consolidated financial statements as of December 31, 2017 and for the year then ended, the Company evaluated subsequent events through August 6, 2018, the date on which these financial statements were issued.

Additional ordinary shares issuance

In 2018, the Company issued 625,511 ordinary shares to third-party licensors as consideration for the in-licensing of technology relevant to its program in settlement of obligations accrued as of December 31, 2017.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Additional Series B issuance

In January 2018, the Company issued 616,641 Series B convertible preferred shares to investors at £4.019 per share for gross proceeds of $3.3 million, of which $1.0 million was received in December 2017 (Note 6).

GSK asset purchase and license agreement

In April 2018, the Company entered into an asset purchase and license agreement (the "GSK Agreement") with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). This complements and enhances the Company's current portfolio.

The portfolio of programs and options acquired consists of:

- Two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS;
- One earlier stage clinical gene therapy program for TDBT;
- Strimvelis, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for mucopolysaccharidosis type 1 ("MPS-I" or "Hurler syndrome"), chronic granulomatous disease ("CGD"), and globoid cell leukodystrophy ("GLD").

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration of £94.2 million ($133.6 million as of date of acquisition), which includes an upfront payment of £10.0 million ($14.2 million at the acquisition date) and 15,563,230 Series B-2 convertible preferred shares of the Company issued to GSK at £65.8 million ($93.4 million at the acquisition date), an inventory purchase liability valued at £4.9 million ($6.9 million) and transaction costs of £0.6 million ($0.8 million). The Company has allocated £94.2 million ($133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development).

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million ($92.4 million) representing the estimated fair value of the Priority Review Vouchers ("PRVs"), and associated liabilities in the amount of £41.9 million ($59.4 million) representing the estimated fair value of the Company's obligations under the GSK Agreement. The Company has since determined that the PRVs and associated liabilities did not meet the criteria for recognition due to their contingent nature based on their dependence of FDA approval of the underlying development program, and accordingly, has corrected this misstatement in the initial accounting for the GSK Agreement as of and for the six months ended June 30, 2018.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The Company is required to use commercially reasonable efforts to obtain a PRV from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDBT, the first of which GSK retained beneficial ownership. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDBT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As described above, the Company has no longer reflected a liability related to the PRV because the contingent liability was not probable and could not be reasonably estimated at the time of the transaction.

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability of £12.9 million ($18.4 million at the acquisition date). This liability will be amortized on a straight-line basis over twenty five months which is the remaining period of expected sales of Strimvelis as a credit to research and development expenses. During the six months ended June 30, 2018, the Company amortized $1.4 million as a credit to research and development expenses. The consideration transferred in the asset acquisition was measured at cost, including transaction costs, assets and equity interests transferred by the acquirer, and liabilities incurred by the acquirer as noted below:

	Consideration (as restated)
	(in thousands)
Upfront cash paid for GSK Agreement	$ 14,186
Series B-2 convertible preferred shares issued to GSK	93,391
Transaction costs	780
Liabilities:	
Strimvelis liability	18,351
Inventory purchase liability	6,893
Total consideration transferred:	$ 133,601

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and the Company-developed product candidate, OTL-101. The Company will also pay tiered royalty rates at percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at percentage from the high single-digits to low double-digit for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

The Company and GSK have also separately executed a Transition Services Agreement ("TSA") as well as an Inventory Sale Agreement, both effective April 11, 2018. The TSA outlines several activities that the Company has requested GSK to assist with during the transition period, including but not limited to utilizing GSK to sell, market and distribute Strimvelis, and assist with regulatory, clinical and non-clinical activities for the other non-commercialized products which were ongoing at the date of the GSK Agreement. The TSA is scheduled to expire in December 2018.

In connection with the Company's entering into the GSK Agreement, GSK assigned rights and obligations to certain contracts, which include among others, the original license agreement with Telethon/Ospedale San Raffaele and an ongoing manufacturing agreement.

Telethon-OSR research and development collaboration and license agreement

In connection with the Company's entering into the GSK Agreement, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDBT, CGD, MPS-I and GLD.

As consideration for the licenses and options granted, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones and pay Telethon-OSR a fee in connection with the exercise of an option for each collaboration program. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement.

Series C issuance

In August 2018, the Company sold 17,421,600 Series C convertible preferred shares at a price of $8.61 per share for gross proceeds of approximately $150.0 million. The rights, preferences and privileges for the Series C convertible preferred shares are similar to those of the convertible preferred shares described in Note 6.

As part of the Series C financing, the Company sold to several of its executives and members of its board of directors Series C convertible preferred shares at a price of $8.61 per share.

Events subsequent to original issuance of financial statements (unaudited)

In connection with the reissuance of the financial statements, the Company has evaluated subsequent events through October 23, 2018, the date the financial statements were reissued.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Grants of stock options under the 2016 Plan

From January 1, 2018 to September 14, 2018, the Company granted options to employees and one of our new directors for the purchase of an aggregate of 3,085,388 ordinary shares, at a weighted average exercise price of $4.97 per share. The aggregate grant-date fair value of these options was $15.6 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

On September 25, 2018, the Company granted options to employees and consultants for the purchase of an aggregate of 242,500 ordinary shares, at a weighted average exercise price of $3.62 per share. The aggregate grant-date fair value of these options was $1.7 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

Orchard Therapeutics Limited
Unaudited condensed consolidated balance sheets
(In thousands, except share and per share amounts)

	December 31, 2017	June 30, 2018 (as restated)	Supplemental Pro forma June 30, 2018 (as restated)
Assets			
Current assets:			
Cash	$ 89,856	$ 48,762	$ 48,762
Other receivables	1,247	428	428
Prepaid expenses and other current assets	3,118	8,863	8,863
Total current assets	94,221	58,053	58,053
Non-current assets:			
Property and equipment, net	2,713	5,342	5,342
Other long-term receivables	360	1,251	1,251
Total non-current assets	3,073	6,593	6,593
Total assets	$ 97,294	$ 64,646	$ 64,646
Liabilities and shareholders' equity			
Current liabilities:			
Accounts payable	$ 3,891	$ 13,614	$ 13,614
Accrued expenses and other current liabilities	6,864	28,669	28,669
Total current liabilities	10,755	42,283	42,283
Other long-term liabilities	134	7,617	7,617
Total liabilities	10,889	49,900	49,900
Commitments and contingencies (*Note 11*)			
Shareholders' equity:			
Convertible preferred shares, £0.00001 par value; 42,198,154 and 57,761,384 shares authorized as of December 31, 2017 and June 30, 2018, respectively; 41,581,513 and 57,761,384 shares issued and outstanding as of December 31, 2017 and June 30, 2018, respectively; nil shares issued and outstanding as of June 30, 2018 (supplemental pro forma)	134,069	229,709	—
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,413 of shares at December 31, 2017 and June 30, 2018, respectively; 11,154,720 and 11,793,356 shares issued and outstanding at December 31, 2017 and June 30, 2018, respectively; 69,554,740 shares issued and outstanding at June 30, 2018 (supplemental pro forma)	—	—	1
Additional paid-in capital	7,610	9,885	239,593
Accumulated other comprehensive income	4,127	6,097	6,097
Accumulated deficit	(59,401)	(230,945)	(230,945)
Total shareholders' equity	86,405	14,746	14,746
Total liabilities and shareholders' equity	$ 97,294	$ 64,646	$ 64,646

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited
Unaudited condensed consolidated statements of operations and comprehensive loss
(In thousands, except share and per share amounts)

	Six months ended June 30,	
	2017	2018 (as restated)
Operating expenses:		
Research and development	$ 10,546	$ 160,162
General and administrative	2,270	11,948
Total operating expenses	12,816	172,110
Loss from operations	(12,816)	(172,110)
Other income (expense):		
Other (expense) income	(400)	401
Total other (expense) income, net	(400)	401
Net loss before income tax	(13,216)	(171,709)
Income tax benefit	42	165
Net loss attributable to ordinary shareholders	$ (13,174)	$ (171,544)
Other comprehensive income		
Foreign currency translation adjustment	2,070	1,970
Total comprehensive loss	$ (11,104)	$ (169,574)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.24)	$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	10,648,967	12,615,109
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.55)	$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted	8,522,366	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shareholders, basic and diluted		$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basis and diluted		49,349,711

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited
Unaudited condensed consolidated statement of shareholders' equity
(In thousands, except share amounts)

	Convertible preferred shares		Ordinary shares		Additional paid-in capital	Accumulated other comprehensive income	Accumulated deficit	Total
	Shares	Amount	Shares	Amount				
Balance at December 31, 2017	**41,581,513**	**$134,069**	**11,154,720**	**$ —**	**$ 7,610**	**$ 4,127**	**$ (59,401)**	**$86,405**
Issuance of convertible preferred shares, net of issuance costs	16,179,871	95,640	—	—	—	—	—	95,640
Exercise of options.	—	—	13,125	—	25	—	—	25
Share-based compensation expense.	—	—	—	—	2,250	—	—	2,250
Ordinary shares issued as part of license agreements.	—	—	625,511	—	—	—	—	—
Foreign currency translation adjustment (as restated)	—	—	—	—	—	1,970	—	1,970
Net loss (as restated)	—	—	—	—	—	—	(171,544)	(171,544)
Balance at June 30, 2018 (as restated).	**57,761,384**	**$229,709**	**11,793,356**	**$ —**	**$ 9,885**	**$ 6,097**	**$ (230,945)**	**$14,746**

See accompanying notes to unaudited condensed consolidated financial statements

Orchard Therapeutics Limited
Unaudited condensed consolidated statements of cash flows
(In thousands, except share amounts)

	Six months ended June 30,	
	2017	2018 (as restated)
Cash flows from operating activities		
Net loss	$ (13,174)	$ (171,544)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	168	504
Share-based compensation	328	2,250
Non-cash consideration for licenses	—	93,391
Changes in components of operating assets and liabilities:		
Other receivables	(7,166)	(122)
Prepaid and other assets	(1,020)	(6,029)
Accounts payable	1,299	9,868
Accrued expenses and other current liabilities	4,933	22,812
Other long-term liabilities	(2)	7,795
Net cash used in operating activities	(14,634)	(41,075)
Cash flows from investing activities		
Purchases of property and equipment	(663)	(2,833)
Net cash used in investing activities	(663)	(2,833)
Cash flows from financing activities		
Proceeds from the issuance of convertible preferred shares, net of issuance costs	44,609	2,250
Proceeds from issuance of ordinary shares	—	25
Net cash provided by financing activities	44,609	2,275
Effect of exchange rate changes on cash	2,102	539
Net increase (decrease) in cash	31,414	(41,094)
Cash—beginning of period	3,497	89,856
Cash—end of period	$ 34,911	$ 48,762
Supplemental disclosure of non-cash investing and financing activities		
Settlement of tranche obligations	$ 1,402	$ —
Property and equipment included in accrued expenses and accounts payable at period end	$ 543	$ 357
Convertible preferred shares issued for licenses	$ —	$ 93,391

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements

Six months ended June 30, 2017 and 2018
(amounts in thousands, except share and per share data)

1. Basis of presentation

Basis of presentation

The accompanying unaudited condensed consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company and its wholly owned subsidiaries, Orchard Therapeutics North America and Orchard Therapeutics Netherlands B.V., after elimination of all intercompany accounts and transactions.

The unaudited condensed consolidated interim financial statements have been prepared on the same basis as the audited annual consolidated financial statements as of and for the year ended December 31, 2017, and, in the opinion of management, reflect all adjustments, consisting of normal recurring adjustments, necessary for the fair statement of the Company's financial position as of June 30, 2018, and the results of its operations and its cash flows for the six months ended June 30, 2017 and 2018.

The results for the six months ended June 30, 2018 are not necessarily indicative of the results to be expected for the year ending December 31, 2018, any other interim periods, or any future year or period. These interim financial statements should be read in conjunction with the audited financial statements as of and for the year ended December 31, 2017, and the notes thereto, which are included elsewhere in this Registration Statement.

Through June 30, 2018, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares. The Company has incurred recurring losses since its inception, including net losses of $13.2 million and $171.5 million for the periods ended June 30, 2017 and 2018, respectively. As of June 30, 2018, the Company had an accumulated deficit of $230.9 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expected that its cash on hand as of June 30, 2018 of $48.8 million, together with the $148.0 million of net cash proceeds received from the Company's sale of Series C convertible preferred shares in August 2018 (Note 13) will be sufficient to fund its operations and capital expenditure requirements through at least 12 months from the issuance date of these unaudited condensed consolidated financial statements.

Restatement of previously reported financial statements

The Company has restated its unaudited condensed consolidated financial statements as of and for the six months ended June 30, 2018, resulting from the determination that certain assets and liabilities related to the GSK asset purchase and license agreement transaction did not meet the criteria for recognition due to their contingent nature based on their dependence on FDA approval of the underlying development program.

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million ($92.4 million) representing the estimated fair value of the Priority Review Vouchers ("PRVs"), and associated liabilities in the amount of £41.9 million ($59.4 million) representing the

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

estimated fair value of the Company's obligations under the GSK agreement. The Company has corrected the misstatement by recording a decrease to intangible assets of £65.1 million ($86.0 million) and decrease to liabilities of £41.9 million ($55.3 million), in each instance as of June 30, 2018, and recording an increase to research and development expenses of £23.2 million ($32.9 million) for the period ended June 30, 2018.

As a result, the Company has restated its unaudited condensed consolidated balance sheet, the related unaudited condensed consolidated statement of operations and comprehensive loss, unaudited condensed consolidated statement of shareholders' equity, and unaudited condensed consolidated statement of cash flows as of and for the period ended June 30, 2018. The impact of these adjustments is detailed in the tables below.

Unaudited condensed consolidated balance sheet

	Previously Reported	Adjustment	As Restated	Supplemental pro forma As Restated
Assets				
Current assets				
Cash	$ 48,762	$ —	$ 48,762	$ 48,762
Other receivables	428	—	428	428
Prepaid expenses and other current assets	8,863	—	8,863	8,863
Total current assets	58,053	—	58,053	58,053
Non-current assets:				
Property and equipment, net	$ 5,342	$ —	$ 5,342	$ 5,342
Intangible assets	86,005	(86,005)	—	—
Other long -term receivables	1,251	—	1,251	1,251
Total non-current assets	92,598	(86,005)	6,593	6,593
Total assets	$ 150,651	$ (86,005)	$ 64,646	$ 64,646
Liabilities and shareholders' equity				
Current liabilities				
Accounts payable	$ 13,614	$ —	$ 13,614	$ 13,614
Accrued expense and other current liabilities	28,669	—	28,669	28,669
Total current liabilities	42,283	—	42,283	42,283
Long-term liabilities				
Other long-term liabilities	62,950	(55,333)	7,617	7,617
Total long-term liabilities	62,950	(55,333)	7,617	7,617
Total liabilities	105,233	(55,333)	49,900	49,900
Commitments and contingencies (Note 11)				

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

	Previously Reported	Adjustment	As Restated	Supplemental pro forma As Restated
Shareholders' equity				
Convertible preferred shares, £0.00001 par value; 42,198,154 and 57,761,384 shares authorized as of December 31, 2017 and June 30, 2018, respectively; 41,581,513 and 57,761,384 shares issued and outstanding as of December 31, 2017 and June 30, 2018, respectively; nil shares issued and outstanding as of June 30, 2018 (pro forma)	229,709	—	229,709	—
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,413 of shares at December 31, 2017 and June 30, 2018, respectively; 11,154,720 and 11,793,356 shares issued and outstanding at December 31, 2017 and June 30, 2018, respectively; 69,554,740 shares issued and outstanding at June 30, 2018 (pro forma)	—	—	—	1
Additional paid-in capital	9,885	—	9,885	239,593
Accumulated other comprehensive income	3,828	2,269	6,097	6,097
Accumulated deficit	(198,004)	(32,941)	(230,945)	(230,945)
Total shareholders' equity	45,418	(30,672)	14,746	14,746
Total liabilities and shareholders' equity	$ 150,651	$ (86,005)	$ 64,646	$ 64,646

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited condensed consolidated statement of operations and comprehensive loss

	Previously Reported	Adjustment	As Restated
Operating expenses:			
Research and development	$ 127,221	$ 32,941	$ 160,162
General and administrative	11,948	—	11,948
Total operating expense	139,169	32,941	172,110
Loss from operations	(139,169)	(32,941)	(172,110)
Other income:			
Other income	401	—	401
Total other income	401	—	401
Net loss before income tax	(138,768)	(32,941)	(171,709)
Income tax benefit	165	—	165
Net loss attributable to ordinary shareholders	$ (138,603)	$ (32,941)	$ (171,544)
Other comprehensive income			
Foreign currency translation adjustment	$ (299)	$ 2,269	$ 1,970
Total comprehensive loss	$ (138,902)	$ (30,672)	$ (169,574)
Net Loss per share attributable to ordinary shareholders, basic and diluted	$ (10.99)	$ (2.61)	$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	12,615,109	—	12,615,109
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted	$ (13.73)	$ (3.26)	$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted	10,095,863	—	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shareholders, basic and diluted	$ (2.81)	$ (0.67)	$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basic and diluted	49,349,711	—	49,349,711

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited condensed consolidate statements of cash flows

	Previously Reported	Adjustment	As Restated
Cash flows from operating activities			
Net loss	$ (138,603)	$ (32,941)	$ (171,544)
Adjustments to reconcile net loss to net cash used in operating activates			
Depreciation expense	504	—	504
Share-based compensation	2,250	—	2,250
Non-cash consideration for licenses	61,229	32,162	93,391
Changes in components of operating assets and liabilities:			
Other receivables	(122)	—	(122)
Prepaids and other assets	(6,029)	—	(6,029)
Accounts payable	9,111	757	9,868
Accrued expenses and other current liabilities	22,812	—	22,812
Other long-term liabilities	7,795	—	7,795
Net cash used in operating activates	(41,053)	(22)	(41,075)
Cash flows from investing activities			
Purchases of property and equipment	(2,833)	—	(2,833)
Net cash used in investing activates	(2,833)	—	(2,833)
Cash Flows from financing activities			
Proceeds from issuance of preferred shares, net of issuance costs	2,250	—	2,250
Proceeds from issuance of common stock	25	—	25
Net cash provided financing activities	2,275	—	2,275
Effect of exchange rate changes on cash and cash equivalents	517	22	539
Net decrease in cash	(41,094)	—	(41,094)
Cash-beginning of period	89,856	—	89,856
Cash-end of period	$ 48,762	$ —	$ 48,762
Supplemental Disclosure of Non-Cash Investing and Financing Activities			
Property and equipment included in accrued expenses and accounts payable at period end	$ 357	$ —	$ 357
Intangible assets included in accounts payable and other long-term liabilities	$ 56,059	$ (56,059)	$ —
Convertible preferred shares issued for intangible assets	$ 32,161	$ (32,161)	$ —
Convertible preferred shares issued for licenses	$ 61,229	$ 32,162	$ 93,391

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

2. Summary of significant accounting policies

The Company's significant accounting policies are disclosed in the audited consolidated financial statements for the year ended December 31, 2017 included in the Company's audited financial statements included within their Form F-1. Since the date of such consolidated financial statements, there have been no changes to the Company's significant accounting policies.

Unaudited pro forma information

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma information represents information for Orchard Therapeutics plc for the six months ended June 30, 2017 and 2018 (as restated).

Unaudited supplemental pro forma information

In the accompanying consolidated statements of operations and comprehensive loss, the unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the six months ended June 30, 2018 has been prepared to give effect to, upon closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

3. Prepaid expenses and other current assets

Prepaid expenses and other current assets consisted of the following:

	December 31, 2017	June 30, 2018
		(in thousands)
Prepaid external research and development costs	$ 763	$ 3,173
VAT receivable	1,042	832
RDEC receivable	871	4,085
Prepaid rent	259	252
Prepaid other	183	521
Total prepaid expenses and other current assets	$ 3,118	$ 8,863

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

4. Property and equipment

Property and equipment consist of the following:

	December 31, 2017	June 30, 2018
		(in thousands)
Property and equipment		
Lab equipment	$ 2,708	$ 4,253
Leasehold improvements	244	1,447
Furniture and fixtures	59	340
Office and IT equipment	12	110
Property and equipment.	$ 3,023	$ 6,150
Less: accumulated depreciation.	(310)	(808)
Property and equipment, net.	$ 2,713	$ 5,342

Depreciation expense in the six months ended June 30, 2017 and 2018 was $0.2 million and $0.5 million, respectively.

5. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31, 2017	June 30, 2018
		(in thousands)
Accrued external research and development expenses	$ 1,834	$ 15,361
Accrued payroll and related expenses	2,090	2,649
Accrued professional fees	394	1,934
Strimvelis liability—current portion	—	8,202
Accrued other	279	523
Deferred UCLA reimbursement	2,267	—
Total accrued expenses and other current liabilities	$ 6,864	$ 28,669

Included within accrued external research and development expenses as of June 30, 2018 was a payable of $6.4 million to GSK relating to the GSK asset purchase and license agreement.

6. Shareholders' equity and convertible preferred shares

Convertible preferred shares

As of June 30, 2018, the Company's Articles of Association (the "Articles"), as further amended and restated (the "2018 Amended Articles"), authorized a total of 57,761,384 convertible preferred shares with a par value of £0.00001 per share, of which 21,000,000 shares have been designated as Series A convertible preferred shares, 21,198,154 shares have been designated as Series B convertible preferred shares and 15,563,230 shares have been designated as Series B-2

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

convertible preferred shares (the “Series B-2 convertible preferred shares”). The Series A, Series B and Series B-2 convertible preferred shares will be collectively referred to as the Convertible Preferred Shares.

Preferred share financings

In January 2018, the Company issued 616,641 Series B convertible preferred shares to investors at £4.019 per share for gross proceeds of $3.3 million, of which $1.0 million was received in December 2017.

In April 2018, the Company issued 15,563,230 Series B-2 convertible preferred shares to GSK pursuant to the Company entering into an asset purchase and license agreement (the “GSK Agreement”) of which the Company valued the Series B-2 convertible preferred shares issued at $93.4 million (Note 8).

As of each balance sheet, the Convertible Preferred Shares consisted of the following:

	December 31, 2017 (in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	$ 26,994	$ 28,337	21,000,000
Series B convertible preferred shares	21,198,154	20,581,513	107,075	111,617	20,581,513
	42,198,154	41,581,513	$134,069	$ 139,954	41,581,513

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2017.

	June 30, 2018 (in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	$ 26,994	$ 27,739	21,000,000
Series B convertible preferred shares	21,198,154	21,198,154	109,324	112,534	21,198,154
Series B-2 convertible preferred shares	15,563,230	15,563,230	93,391	82,620	15,563,230
	57,761,384	57,761,384	$229,709	$ 222,893	57,761,384

(a) Amounts were translated into United States dollars using the spot rate as of June 30, 2018.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The holders of the Convertible Preferred Shares as of June 30, 2018 have the same rights and preference disclosed in the Company's annual financial statements with the exception of certain voting rights related to Series B-2 convertible preferred shares as described below:

Voting

Each Series A and Series B share shall confer one right to vote at all general meetings and to receive and vote on proposed written resolutions of the Company. In respect of the Series B-2 convertible preferred shares only fifty percent of the total number of Series B-2 convertible preferred shares held by GSK shall be treated as having voting rights and all remaining Series B-2 convertible preferred shares in issue shall be disregarded for purposes of voting at any general meeting of the Company or for the purposes of any proposed written resolutions.

Ordinary shares

Ordinary share issuances

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. In 2018, the Company issued 437,049 ordinary shares to third-party licensors as consideration for the in-licensing of technology relevant to its program in settlement of obligations accrued as of December 31, 2017.

In June 2018, the Company issued 188,462 ordinary shares to Oxford BioMedica for a milestone that was achieved in November 2017.

As of December 31, 2017 and June 30, 2018, the Company had outstanding 11,154,720 and 11,793,356 ordinary shares, respectively.

7. Share-based compensation

2016 Share option plan

In September 2016, the Company adopted the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"). The 2016 Plan provides for the Company to grant incentive and non-qualified options to officers, directors, consultants, and advisors to purchase the Company's ordinary shares.

The total number of ordinary shares that may be issued under the 2016 Plan was 11,800,000 shares as of June 30, 2018 of which 2,433,172 shares remained available for future grant.

During the six months ended June 30, 2017 and 2018, the Company granted options to purchase 528,100 and 4,384,781 shares of ordinary shares, respectively, to employees, nonemployees and directors. The Company recorded share-based compensation expense for options granted to employees, nonemployees and directors of $0.3 million and $2.2 million during the six months ended June 30, 2017 and 2018, respectively.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Option valuation

When utilizing the Black-Scholes option-pricing model to determine the grant date fair value of share options granted in the six months ended June 30, 2017 and 2018, the Company used the following assumptions:

Employee, Nonemployees and directors

	Six months ended June 30,	
	2017	**2018**
Risk-free interest rate	2.13%	2.66% - 2.83%
Expected term (in years)	6.08	6.08
Expected volatility	80.00%	66.51% - 68.17%
Expected dividend rate	0.00%	0.00%

Options

The following table summarizes option activity under the 2016 Plan since December 31, 2017:

	Shares	**Weighted average exercise price**	**Weighted average remaining contractual life**	**Aggregate intrinsic value**
			(in thousands, except share and per share amounts)	
Options outstanding at December 31, 2017	5,223,443	$ 0.96	9.28	$ 10,483
Granted	4,382,511	1.67		
Exercised	(13,125)	1.95		
Cancelled	(226,001)	0.49		
Options outstanding at June 30, 2018	9,366,828	$ 1.30	9.21	$ 36,803
Vested as of June 30, 2018	1,394,330	$ 0.22	8.33	$ 6,964

The weighted average exercise price of options granted to United Kingdom employees in the six months ended June 30, 2018 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees in the six months ended June 30, 2018 was $2.51.

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares.

The weighted average grant date fair value of the options granted during the six months ended June 30, 2017 and 2018, was $1.63 per share and $3.34 per share, respectively.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Share-based compensation

Share-based compensation expense was classified in the consolidated statements of operations and comprehensive loss as follows:

	Six months ended June 30,	
	2017	2018
	(in thousands)	
Research and development	$ 247	$ 674
General and administrative	81	1,576
Total	$ 328	$ 2,250

The Company had 7,974,768 unvested options outstanding as of June 30, 2018. As of June 30, 2018, there was $17.1 million of unrecognized compensation expense related to unvested options, that is expected to be recognized over a weighted average period of approximately 3.25 years.

8. License and research arrangements

GSK asset purchase and license agreement

In April 2018, the Company entered into an asset purchase and license agreement (the “GSK Agreement”) with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital (“Telethon-OSR”). This complements and enhances the Company’s current portfolio.

The portfolio of programs and options acquired consists of:

- Two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS;
- One earlier stage clinical gene therapy program for TDBT;
- Strimvelis, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for mucopolysaccharidosis type 1 (“MPS-I” or “Hurler syndrome”), chronic granulomatous disease (“CGD”), and globoid cell leukodystrophy (“GLD”).

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration of £94.2 million ($133.6 million as of date of acquisition), which includes an upfront payment of £10.0 million ($14.2 million at the acquisition date) and 15,563,230 Series B-2 convertible preferred shares of the Company issued to GSK valued at £65.8 million ($93.4 milion at the acquisition date), an inventory purchase liability

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

valued at £4.9 million ($6.9 million) and transaction costs of £0.6 million ($0.8 million). The Company has allocated £94.2 million ($133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development).

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million ($92.4 million) representing the estimated fair value of the Priority Review Vouchers ("PRVs"), and associated liabilities in the amount of £41.9 million ($59.4 million) representing the estimated fair value of the Company's obligations under the GSK Agreement. The Company has since determined that the PRVs and associated liabilities did not meet the criteria for recognition due to their contingent nature based on their dependence of FDA approval of the underlying development program, and accordingly, has corrected this misstatement in the initial accounting for the GSK Agreement as of and for the six months ended June 30, 2018.

The Company is required to use commercially reasonable efforts to obtain a PRV from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDBT and to, the first of which GSK retained beneficial ownership. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDBT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As described above, the Company has no longer reflected a liability related to the PRV because the contingent liability was not probable and could not be reasonably estimated at the time of the transaction.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability of £12.9 million ($18.4 million at the acquisition date). This liability will be amortized on a straight-line basis over twenty five months which is the remaining period of expected sales of Strimvelis as a credit to research and development expenses. During the six months ended June 30, 2018, the Company amortized $1.4 million as a credit to research and development expenses. The consideration transferred in the asset acquisition was measured at cost, including transaction costs, assets and equity interests transferred by the acquirer, and liabilities incurred by the acquirer as noted below:

	Consideration (as restated)
	(in thousands)
Upfront cash paid for GSK Agreement	$ 14,186
Series B-2 convertible preferred shares issued to GSK	93,391
Transaction costs	780
Liabilities:	
Strimvelis liability	18,351
Inventory purchase liability	6,893
Total consideration transferred:	$ 133,601

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and the Company-developed product candidate, OTL-101. The Company will also pay tiered royalty rates at percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at percentage from the high single-digits to low double-digit for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The Company and GSK have also separately executed a Transition Services Agreement ("TSA") as well as an Inventory Sale Agreement, both effective April 11, 2018. The TSA outlines several activities that the Company has requested GSK to assist with during the transition period, including but not limited to utilizing GSK to sell, market and distribute Strimvelis, and assist with regulatory, clinical and non-clinical activities for the other non-commercialized products which were ongoing at the date of the GSK Agreement. The TSA is scheduled to expire in December 2018.

In connection with the Company's entering into the GSK Agreement, GSK assigned rights and obligations to certain contracts, which include among others, the original license agreement with Telethon/Ospedale San Raffaele and an ongoing manufacturing agreement.

Telethon-OSR research and development collaboration and license agreement

In connection with the Company's entering into the GSK Agreement, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDBT, CGD, MPS-I and GLD.

The Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones and pay Telethon-OSR a fee in connection with the exercise of an option for each collaboration program. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement. In aggregate, the Company may pay up to $120.3 million of milestone payments upon achievement of certain product development milestones and exercises of options under the Telethon-OSR agreements.

UCLB/UCLA License Agreement

In February 2016, and amended in July 2017, the Company entered into the UCLB/UCLA License Agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of $0.8 million for the license to the joint UCLB/UCLA technology and $1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 5,829,545 ordinary shares to UCLB, of which 4,300,000 and 1,529,545 ordinary shares were issued in 2016 and 2017, respectively. The Company recorded research and development expense based on the fair value of the ordinary shares as of the time the agreement was executed. The Company was also obligated to make an additional cash payment for clinical data. In 2017, the Company paid $0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of $0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company is obligated to make payments to the parties of up to an aggregate of $38.9 million upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

The Company recorded $0.1 million for research and development costs in the six months ended June 30, 2017 and 2018.

Unless terminated earlier by either party, the UCLB/UCLA License Agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors for the Company (“Oxford BioMedica Agreement”). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved and the Company was committed to issue 188,462 ordinary shares in 2018. As of June 30, 2018, the Company’s remaining potential share obligation under the agreement comprised one milestone, which, upon achievement, would require the Company to issue additional ordinary shares.

The Company recorded $0.5 million to research and development expense upon execution of the Oxford BioMedica Agreement in 2016 and $0.1 million upon achievement of the first development milestone in 2017. The expense was determined based on the ordinary shares’ fair value as of the time the agreement was executed. There were no amounts recorded to research and development expense in the six months ended June 30, 2017 and 2018 related to the Oxford BioMedica Agreement.

The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

Other license and research agreements

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. As part of the consideration related to these license agreements, the total share commitment was 1,288,000 and 469,049 ordinary shares and the Company made cash payments of $2.7 million and $0.4 million in 2016 and 2017, respectively. The Company recorded nil and $0.6 million to research and development expense in the six months ended June 30, 2017

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

and 2018, respectively. In addition, the Company also committed to make certain clinical and regulatory milestone payments in the aggregate of $31.8 million as well as single-digit percent royalties on net sales of products and services associated with in-licensed technology.

UCLA research agreement

In January 2017, the Company and UCLA executed a subcontract agreement ("UCLA Research Agreement"), whereby the Company would provide UCLA certain research and development services related to autologous lentiviral gene therapy in ADA-SCID as part of UCLA's existing ADA-SCID research program that is being funded by the California Institute for Regenerative Medicine ("CIRM"). The total reimbursement the Company may receive under the UCLA Research Agreement is $10.4 million, which may be received during the period from January 2017 to December 2021. The reimbursement is recognized as a reduction in research and development expense for research activities that have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. In the event the Company has performed reimbursable research activities and has not been reimbursed, it is recognized within prepaid expenses and other current assets. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM.

In the six months ended June 30, 2017 and 2018, the Company recorded $3.7 million and $2.4 million as a reduction of research and development expenses related to the UCLA Research Agreement. As of June 30, 2018, the Company recorded $0.2 million within prepaid expenses and other current assets on the Company's condensed consolidated balance sheet related to research activities performed that have not reimbursed.

9. Income Taxes

The benefit for income taxes for the six months ended June 30, 2017 and 2018 was $42,000 and $165,000, respectively. The tax benefit for the six months ended June 30, 2018 consisted primarily of the reversal of a deferred tax liability in the United States.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets, which are comprised primarily of net operating loss carryforwards and research and development credits. Management has considered the Company's history of cumulative net losses in the United States and United Kingdom, estimated future taxable income and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of its United States and United Kingdom deferred tax assets. Accordingly, the Company maintains a full valuation allowance against these net deferred tax assets as of June 30, 2018.

The Company files tax returns in the United States, various states, and foreign jurisdictions. With few exceptions, the Company is subject to U.S. federal, state and local, and foreign tax examinations by tax authorities for years 2016 through present. As of June 30, 2018, the Company has not recorded a liability for unrecognized tax benefits, interest, or penalties related to federal, state, and foreign income tax matters and there currently no pending tax examinations.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The research and development tax credit received in the United Kingdom is recorded as a credit against R&D expenses. The UK research and development tax credit, as described below, is fully refundable to the Company and is not dependent on current or future taxable income. As a result, the Company has recorded the entire benefit from the UK research and development tax credit as a reduction to R&D expenses and is not reflected as part of the income tax provision. If, in the future, any UK research and development tax credits generated are needed to offset a corporate income tax liability in the UK, that portion would be recorded as a benefit within the income tax provision and any refundable portion not dependent on taxable income would continue to be recorded as a reduction to research and development expenses.

As a company that carries out extensive research and development activities, the Company seeks to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises Research and Development Tax Credit Program (“SME Program”) and the Research and Development Expenditure program (“RDEC Program”). Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income. Such credits are accounted as reductions in research and development expense in the period in which the expenditures were incurred.

Based on criteria established by HM Revenue and Customs (“HMRC”), management of the Company expects a proportion of expenditures being carried in relation to its pipeline research, clinical trials management and manufacturing development activities to be eligible for the RDEC Program for the six months ended June 30, 2017 and 2018. The Company will assess whether it is possible to qualify under the more favorable SME Program for future accounting periods, but this may be affected as a result of becoming a United States public company.

The Company has recorded United Kingdom research and development tax credit as an offset to research and development expense in the consolidated statements of operations and comprehensive loss of $0.2 million and $3.6 million for the periods ended June 30, 2017 and 2018, respectively. As of June 30, 2018, the Company’s tax incentive receivable from the United Kingdom government was $4.1 million. These amounts have not yet been paid to the Company by HMRC.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

10. Net loss per share

The following table sets forth the computation of basic and diluted net loss per share:

	Six months ended June 30,	
	2017	2018 (as restated)
	(In thousands, except per share and share amounts)	
Net loss	$ (13,174)	$ (171,544)
Net loss attributable to ordinary shareholders	$ (13,174)	$ (171,544)
Weighted average ordinary shares outstanding, basic and diluted	10,648,967	12,615,109
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.24)	$ (13.60)

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all shares convertible into ordinary shares outstanding would have been anti-dilutive.

The following securities are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti- dilutive:

	Six Months Ended June 30,	
	2017	2018
Convertible preferred shares	28,254,000	57,761,384
Share options	2,408,482	9,070,186
	30,662,482	66,831,570

In August 2018, the Company issued 17,421,600 Series C convertible preferred shares (Note 13).

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited pro forma net loss per share attributable to ordinary shareholders

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. The following represents pro forma earnings per share information for Orchard Therapeutics plc for the six months ended June 30, 2017 and 2018 (as restated):

	Six months ended June 30,	
	2017	2018 (as restated)
	(in thousands except per share and share amounts)	
Net loss attributable to ordinary shareholders	$ (13,174)	$ (171,544)
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	$ (1.55)	$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	8,522,366	10,095,863

Unaudited supplemental pro forma net loss per share attributable to ordinary shareholders

The unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the six months ended June 30, 2018 (as restated) have been prepared to give effect to adjustments arising upon the closing of a qualified IPO, (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

A reconciliation of the pro forma weighted-average number of ordinary shares used in computing supplemental pro forma basic and diluted net loss per share applicable to ordinary shareholders is as follows:

	Six months ended June 30, 2018 (as restated)
	(in thousands except per share and share amounts)
Numerator:	
Net loss attributable to ordinary shareholders	$ (171,544)
Denominator	
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	10,095,863
Pro forma adjustment to reflect assumed conversion of preferred share into ordinary share (unaudited)	39,253,848
Supplemental pro forma weighted average number of ordinary shares used in computing supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	49,349,711
Supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	$ (3.48)

11. Commitments and contingencies

Lease agreements

In October 2016, the Company entered into a lease agreement for five years for laboratory space in Foster City, California, United States. The lease commencement date was October 1, 2016. The Company was provided with one month of free rent.

In January 2017, the Company entered into a lease agreement for office space in London, United Kingdom. The lease commenced on January 16, 2017 and expires on January 16, 2019. Management has the option to terminate the lease at its discretion after at the end of the one year anniversary of the lease.

In November 2017, the Company entered into a lease arrangement for laboratory space in Menlo Park, California, United States. The lease commenced on November 1, 2017 and expires on November 30, 2020. The Company was provided with one month of free rent.

In January 2018, the Company leased office space in London, United Kingdom. The lease has a term of five years and terminates in January 2023. The annual rental commitment approximates $0.8 million.

In March 2018, the Company leased office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental commitment approximates $0.3 million.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The Company recognizes rent expense on a straight-line basis over the respective lease period and has recorded deferred rent for rent expense incurred but not yet paid.

The Company recorded rent expense of $0.3 million and $1.2 million in the six months ended June 30, 2017 and 2018, respectively.

License agreements

The Company has entered into several license agreements (Note 8). In connection with these agreements the Company is required to make a number of milestone payments and annual license maintenance payments. The Company evaluated all milestone payments within the arrangements to estimate the probability of the Company meeting the milestones. The Company concluded in November 2017 a milestone relating to the Oxford BioMedica Agreement was met (Note 8), and as a result, the associated milestone consideration of $0.1 million was recorded to research and development expense in the year ended December 31, 2017. The Company determined that no milestone payments were probable as of June 30, 2018.

Commitment with contract manufacturing organization

The Company has entered into agreements with contract manufacturing organizations relating to the provision of manufacturing services and purchase of clinical material to be used in clinical trials that include minimum purchase commitments. As of June 30, 2018, $1.1m (2017: nil) included within prepayments relates to prepaid instalments against these minimum commitments. The Company is committed to make further payments totaling $9.2 million between September 2018 and March 2020.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

12. Benefit plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to five percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid $0.1 million and $ 0.2 million in matching contributions in the six months ended June 30, 2017 and 2018, respectively.

13. Subsequent events

The Company evaluated subsequent events through September 14, 2018, the date on which these financial statements were issued.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Telethon-OSR research and development collaboration and license agreement

In July 2018, the first patient was enrolled and dosed in the MPS-1 clinical study which In accordance with the license agreement triggered a milestone payment of $1.8 million payable by the Company.

Series C issuance

In August 2018, the Company sold 17,421,600 Series C convertible preferred shares at a price of $8.61 per share for net proceeds of approximately $148.0 million. The rights, preferences and privileges for the Series C convertible preferred shares are similar to those of the convertible preferred shares described in Note 6.

As part of the Series C financing, the Company sold 406,504 shares of Series C convertible preferred shares at a price of $8.61 per share to several of its executives and members of its board of directors for proceeds of $3.5 million.

Grants of stock options under the 2016 Plan

From July 1, 2018 to September 14, 2018, the Company granted options to employees and one of our new directors for the purchase of an aggregate of 3,085,388 ordinary shares, at a weighted average exercise price of $4.97 per share. The aggregate grant-date fair value of these options was $15.6 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

On September 25, 2018, the Company granted options to employees and consultants for the purchase of an aggregate of 242,500 ordinary shares, at a weighted average exercise price of $3.62 per share. The aggregate grant-date fair value of these options was $1.7 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

Events subsequent to original issuance of financial statements

In connection with the reissuance of the financial statements, the Company has evaluated subsequent events through October 23, 2018, the date the financial statements were reissued.

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American Depositary Shares
Representing Ordinary Shares

PRELIMINARY PROSPECTUS

J.P. Morgan
Goldman Sachs & Co. LLC
Cowen
Wedbush PacGrow

, 2018

Through and including , 2018 (the 25th day after the date of this prospectus), all dealers that effect transactions in these securities, whether or not participating in this offering, may be required to deliver a prospectus. This is in addition to the dealers' obligation to deliver a prospectus when acting as underwriters and with respect to their unsold allotments or subscriptions.

PART II

INFORMATION NOT REQUIRED IN PROSPECTUS

Item 6. Indemnification of Directors and Officers.

Subject to the Companies Act 2006, members of the registrant's board of directors and its officers (excluding auditors) have the benefit of the following indemnification provisions in the registrant's Articles of Association:

Current and former members of the registrant's board of directors or officers shall be reimbursed for:

(i) all costs, charges, losses, expenses and liabilities sustained or incurred in relation to his or her actual or purported execution of his or her duties in relation to the registrant, including any liability incurred in defending any criminal or civil proceedings; and

(ii) expenses incurred or to be incurred in defending any criminal or civil proceedings, in an investigation by a regulatory authority or against a proposed action to be taken by a regulatory authority, or in connection with any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company, or collectively the Statutes, arising in relation to the registrant or an associated company, by virtue of the actual or purposed execution of the duties of his or her office or the exercise of his or her powers.

In the case of current or former members of the registrant's board of directors, there shall be no entitlement to reimbursement as referred to above for (i) any liability incurred to the registrant or any associated company,(ii) the payment of a fine imposed in any criminal proceeding or a penalty imposed by a regulatory authority for non-compliance with any requirement of a regulatory nature, (iii) the defense of any criminal proceeding if the member of the registrant's board of directors is convicted, (iv) the defense of any civil proceeding brought by the registrant or an associated company in which judgment is given against the director, and (v) any application for relief under the statutes of the United Kingdom and any other statutes that concern and affect the registrant as a company in which the court refuses to grant relief to the director.

In addition, members of the registrant's board of directors and its officers who have received payment from the registrant under these indemnification provisions must repay the amount they received in accordance with the Statutes or in any other circumstances that the registrant may prescribe or where the registrant has reserved the right to require repayment.

The underwriting agreement the registrant will enter into in connection with the offering of ADSs being registered hereby provides that the underwriters will indemnify, under certain conditions, the registrant's board of directors and its officers against certain liabilities arising in connection with this offering.

Item 7. Recent Sales of Unregistered Securities.

In the three year preceding the filing of this registration statement, we have issued the following securities that were not registered under the Securities Act. All share and per share information presented in this Item 7 does not reflect the 1-for-0.8003 reverse split that will be part of our corporate reorganization:

(a) Issuances of Share Capital

In September 2015, Orchard Therapeutics Limited issued one ordinary share of £1.00 nominal value to one investor for consideration of £1.00 which share, on December 17, 2015, was subdivided into 100,000 ordinary shares of £0.00001 nominal value.

In December 2015, Orchard Therapeutics Limited issued 2,500,000 ordinary shares to one investor for aggregate consideration of £25.00.

In December 2015, Orchard Therapeutics Limited issued 770,175 ordinary shares to two individuals for aggregate consideration of £7.70.

In February 2016, Orchard Therapeutics Limited issued 4,300,000 shares to one investor as consideration for entering into a license agreement.

In April 2016, Orchard Therapeutics Limited issued 1,000,000 ordinary shares to three investors and three individuals as consideration for entering into a license agreement.

In December 2016, Orchard Therapeutics Limited issued 735,000 ordinary shares to one investor as consideration for entering into a license agreement.

In February 2017, Orchard Therapeutics Limited issued 320,000 ordinary shares to one investor for aggregate consideration of £3.20.

In March 2017, Orchard Therapeutics Limited issued 825,000 ordinary shares to one investor as consideration for satisfying a milestone under a license agreement.

In each of November 2017 and August 2018, Orchard Therapeutics Limited issued 188,462 ordinary shares to one investor as consideration for satisfying a milestone under a license agreement.

In December 2017, Orchard Therapeutics Limited issued 704,545 ordinary shares to one investor as consideration for satisfying a milestone under a license agreement.

In February 2018, Orchard Therapeutics Limited issued 437,049 ordinary shares to one investor as consideration for entering into a license agreement.

In February 2016, with subsequent closings in May 2016, July 2016, August 2016, January 2017 and February 2017, Orchard Therapeutics Limited issued an aggregate of 21,000,000 Series A convertible preferred shares to two investors for aggregate consideration of £21.0 million.

In March 2017, with subsequent closings in August 2017, October 2017, December 2017 and January 2018, Orchard Therapeutics Limited issued an aggregate of 21,198,154 Series B convertible preferred shares to 17 investors for aggregate consideration of £85.2 million.

In April 2018, Orchard Therapeutics Limited issued an aggregate of 15,563,230 Series B-2 convertible preferred shares to GSK pursuant to the terms of an asset purchase and license agreement.

In August 2018, Orchard Therapeutics Limited issued an aggregate of 17,421,600 Series C convertible preferred shares to 60 investors for aggregate consideration of approximately $150.0 million.

No underwriters were involved in the foregoing sales of securities. The sales of securities described above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act, including Regulation D and Rule 506 promulgated thereunder, as transactions by an issuer not involving a public offering. All of the purchasers in these transactions represented to us in connection with their purchase that they were acquiring the securities for investment and not distribution, that they could bear the risks of the investment and could hold the securities for an indefinite period of time. Such purchasers received written disclosures that the securities had not been registered under the Securities Act and that any resale must be made pursuant to a registration or an available exemption from such registration. All of the foregoing securities are deemed restricted securities for the purposes of the Securities Act.

(b) Grants and Exercises of Options and Restricted Share Awards

We have granted share options to purchase an aggregate of 13,056,620 ordinary shares, with exercise prices ranging from £0.00001 to $8.24 per share, to employees and directors pursuant to the 2016 Plan. In May 2018, Orchard Therapeutics Limited issued 17,552 ordinary shares to two individuals upon exercise of options for an aggregate purchase price of $27,276.

The issuances of the securities described above were deemed to be exempt from registration pursuant to Section 4(a)(2) of the Securities Act or Rule 701 promulgated under the Securities Act as transactions pursuant to compensatory benefit plans. The ordinary shares issued upon the exercise of options are deemed to be restricted securities for purposes of the Securities Act.

Item 8. Exhibits and Financial Statement Schedules

(a) Exhibits

Exhibit number	Description of exhibit
1.1	Form of Underwriting Agreement.
2.1†	Asset Purchase and License Agreement, by and among the registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Ltd., dated April 11, 2018 (schedules, exhibits, and similar supporting attachments are omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request).
3.1	Form of Articles of Association of Orchard Therapeutics plc (to be effective upon completion of this offering).
4.1	Form of Deposit Agreement.
4.2	Form of American Depositary Receipt (included in exhibit 4.1).
5.1	Opinion of Goodwin Procter (UK) LLP.
10.1*	Investment and shareholders' agreement by and between the registrant and the shareholders named therein, dated August 2, 2018.

Exhibit number	Description of exhibit
10.2#*	2016 Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan, as amended.
10.3#	2018 Share Option and Incentive Plan (to be effective upon effectiveness of this registration statement).
10.4†	Deed of Novation, by and among the registrant, Glaxo Group Limited, GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline S.p.A., Fondazione Telethon and Ospedale San Raffaele (in its own capacity and as successor in interest to Fondazione Centro San Raffaele Del Monte Tabor), dated April 5, 2018.
10.5†	Research and Development Collaboration and License Agreement, by and among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended.
10.6#*	Form of Deed of Indemnity between the registrant and each of its directors and executive officers.
10.7*	Lease Agreement, dated as of January 19, 2018, by and between the Registrant and New Connect Investments Limited.
10.8† *	License and Development Agreement, by and between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended.
10.9† *	License Agreement between UCL Business Plc, The Regents of the University of California and the registrant, dated February 6, 2016, as amended.
10.10#	2018 Employee Share Purchase Plan (to be effective upon effectiveness of this registration statement).
10.11	Director Nomination Agreement, dated as of October 18, 2018, by and between the registrant and Glaxo Group Limited.
21.1*	Subsidiaries of the registrant.
23.1	Consent of independent registered public accounting firm.
23.2	Consent of Goodwin Procter (UK) LLP (included in exhibit 5.1).
24.1*	Power of Attorney (included on signature page to this registration statement).

† Confidential treatment has been requested for portions of this exhibit. These portions have been omitted from the registration statement and filed separately with the United States Securities and Exchange Commission.

* Previously filed.

# Indicates a management contract or any compensatory plan, contract or arrangement.

(b) Financial Statement Schedules

None. All schedules have been omitted because the information required to be set forth therein is not applicable or has been included in the consolidated financial statements and notes thereto.

Item 9. Undertakings.

The undersigned registrant hereby undertakes to provide to the underwriters at the closing specified in the underwriting agreements, certificates in such denominations and registered in such names as required by the underwriters to permit prompt delivery to each purchaser.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers and controlling persons of the registrant pursuant to the provisions described in Item 6 hereof, or otherwise, the registrant has been advised that in the opinion of the SEC

such indemnification is against public policy as expressed in the Securities Act and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act and will be governed by the final adjudication of such issue.

The undersigned registrant hereby undertakes that:

(i) For purposes of determining any liability under the Securities Act, the information omitted from the form of prospectus filed as part of this registration statement in reliance upon Rule 430A and contained in a form of prospectus filed by the registrant pursuant to Rule 424(b)(1) or (4) or 497(h) under the Securities Act shall be deemed to be part of this registration statement as of the time it was declared effective.

(ii) For the purpose of determining any liability under the Securities Act, each post-effective amendment that contains a form of prospectus shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial *bona fide* offering thereof.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, as amended, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form F-1 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of London, United Kingdom, on October 23, 2018.

ORCHARD RX LIMITED

By: /s/ Mark Rothera
Mark Rothera
President and Chief Executive Officer

Pursuant to the requirements of the Securities Act, this registration statement has been signed by the following persons in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Mark Rothera Mark Rothera	President, Chief Executive Officer and Director *(Principal Executive Officer)*	October 23, 2018
/s/ Frank E. Thomas Frank E. Thomas	Chief Financial Officer and Chief Business Officer *(Principal Financial Officer and Principal Accounting Officer)*	October 23, 2018
* James A. Geraghty	Chairman of the Board of Directors	October 23, 2018
* Joanne T. Beck, Ph.D.	Director	October 23, 2018
* Marc Dunoyer	Director	October 23, 2018
* Jon Ellis, Ph.D.	Director	October 23, 2018
* Bobby Gaspar, M.D., Ph.D.	Director	October 23, 2018
* Alex Pasteur, Ph.D.	Director	October 23, 2018
* Charles A. Rowland, Jr.	Director	October 23, 2018
* Hong Fang Song	Director	October 23, 2018
* Elise Wang	Director	October 23, 2018

Cogency Global Inc.

By:	/s/ Tais Laureano Name: Tais Laureano Title: Assistant Secretary on behalf of Cogency Global Inc.	Authorized Representative in the United States	October 23, 2018
* By:	/s/ Frank E. Thomas Frank E. Thomas Attorney-in-fact		

Exhibit 1.1

ORCHARD THERAPEUTICS PLC

[●] American Depositary Shares,
representing [●] Ordinary Shares

Underwriting Agreement

[●], 2018

J.P. Morgan Securities LLC
Goldman Sachs & Co. LLC
Cowen and Company, LLC

As Representatives of the
several Underwriters listed
in Schedule 1 hereto

c/o J.P. Morgan Securities LLC
383 Madison Avenue
New York, New York 10179

c/o Goldman Sachs & Co. LLC
200 West Street
New York, New York 10282-2198

c/o Cowen and Company, LLC
599 Lexington Avenue
New York, New York 10022

Ladies and Gentlemen:

Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales (the "Company"), proposes to issue and sell to the several underwriters listed in Schedule 1 hereto (the "Underwriters"), for whom you are acting as representatives (the "Representatives"), an aggregate of [●] American Depositary Shares ("ADSs"), representing [●] ordinary shares, nominal value £0.10 per share (the "Ordinary Shares"), of the Company (the "Underwritten ADSs") and, at the option of the Underwriters, up to an additional [●] ADSs, representing [●] Ordinary Shares (the "Option ADSs"). The Underwritten ADSs and the Option ADSs are herein referred to as the "Offered ADSs." The Ordinary Shares represented by the Underwritten ADSs are herein referred to as the "Underwritten Shares," the Ordinary Shares represented by the Option ADSs are herein referred to as the "Option Shares" and the Underwritten Shares and Option Shares are herein together referred to as the "Shares."

The Offered ADSs are to be issued pursuant to a deposit agreement (the "Deposit Agreement"), to be dated as of the date hereof, among the Company, Citibank, N.A. as depositary (the "Depositary"), and the owners and beneficial owners from time to time of the ADSs. Each Offered ADS will initially represent the right to receive one Ordinary Share deposited pursuant to the Deposit Agreement.

[●] (the "Directed ADS Underwriter") has agreed to reserve a portion of the Offered ADSs to be purchased by it under this Agreement, up to [●] Offered ADSs, for sale to the Company's directors, officers, and certain employees and other parties related to the Company (collectively, "Participants"), as set forth in the Prospectus (as hereinafter defined) under the heading "Underwriting" (the "Directed ADS Program"). The Offered ADSs to be sold by the Directed ADS Underwriter and its affiliates pursuant to the Directed ADS Program are referred to hereinafter as the "Directed ADSs". Any Directed ADSs not orally confirmed for purchase by any Participant by [●] [A/P].M., New York City time on the business day on which this Agreement is executed will be offered to the public by the Underwriters as set forth in the Prospectus.

As described more fully in the Prospectus, in connection with and prior to the completion of the offering contemplated by this Agreement, (i) all of the issued shares in Orchard Therapeutics (Europe) Limited, a private limited company incorporated under the laws of England and Wales, will be exchanged for the same number and classes of shares in the Orchard Rx Limited, a private limited company incorporated under the laws of England and Wales, (ii) Orchard Rx Limited will be re-registered as a public limited company incorporated under the laws of England and Wales and change its name to Orchard Therapeutics plc, and (iii) all of the issued shares in the Company will be converted into a single class of ordinary shares, nominal value £0.10 per share (collectively, the "Corporate Reorganization").

The Company hereby confirms its agreement with the several Underwriters concerning the purchase and sale of the Offered ADSs, as follows:

1. Registration Statement. The Company has prepared and filed with the Securities and Exchange Commission (the "Commission") under the Securities Act of 1933, as amended, and the rules and regulations of the Commission thereunder (collectively, the "Securities Act"), a registration statement on Form F-1 (File No. 333-227698), including a prospectus, relating to the Offered ADSs. Such registration statement, as amended at the time it became effective, including the information, if any, deemed pursuant to Rule 430A, 430B or 430C under the Securities Act to be part of the registration statement at the time of its effectiveness ("Rule 430 Information"), is referred to herein as the "Registration Statement"; and as used herein, the term "Preliminary Prospectus" means each prospectus included in such registration statement (and any amendments thereto) before effectiveness, any prospectus filed with the Commission pursuant to Rule 424(a) under the Securities Act and the prospectus included in the Registration Statement at the time of its effectiveness that omits Rule 430 Information, and the term "Prospectus" means the prospectus in the form first used (or made available upon request of purchasers pursuant to Rule 173 under the Securities Act) in connection with confirmation of sales of the Offered ADSs. If the Company has filed an abbreviated registration statement pursuant to Rule 462(b) under the Securities Act (the "Rule 462 Registration Statement"), then any reference herein to the term "Registration Statement" shall be deemed to include such Rule 462 Registration Statement. Capitalized terms used but not defined herein shall have the meanings given to such terms in the Registration Statement and the Prospectus.

At or prior to the Applicable Time (as defined below), the Company had prepared the following information (collectively with the pricing information set forth on Annex A, the "Pricing Disclosure Package"): a Preliminary Prospectus dated [●], 2018 and each "free-writing prospectus" (as defined pursuant to Rule 405 under the Securities Act) listed on Annex A hereto.

"Applicable Time" means [●] [A/P].M., New York City time, on [●], 2018.

2. Purchase of the ADSs.

(a) The Company agrees to issue and sell the Underwritten ADSs to the several Underwriters as provided in this underwriting agreement (this "Agreement"), and each Underwriter, on the basis of the representations, warranties and agreements set forth herein and subject to the conditions set forth herein, agrees, severally and not jointly, to purchase at a price per ADS of $[●] (the "Purchase Price") from the Company the respective number of Underwritten ADSs set forth opposite such Underwriter's name in Schedule 1 hereto.

In addition, the Company agrees to issue and sell the Option ADSs to the several Underwriters as provided in this Agreement, and the Underwriters, on the basis of the representations, warranties and agreements set forth herein and subject to the conditions set forth herein, shall have the option to purchase, severally and not jointly, from the Company the Option ADSs at the Purchase Price less an amount per ADS equal to any dividends or distributions declared by the Company and payable on the Underwritten ADSs but not payable on the Option ADSs.

If any Option ADSs are to be purchased, the number of Option ADSs to be purchased by each Underwriter shall be the number of Option ADSs which bears the same ratio to the aggregate number of Option ADSs being purchased as the number of Underwritten ADSs set forth opposite the name of such Underwriter in Schedule 1 hereto (or such number increased as set forth in Section 10 hereof) bears to the aggregate number of Underwritten ADSs being purchased from the Company by the several Underwriters, subject, however, to such adjustments to eliminate any fractional ADSs as the Representatives in their sole discretion shall make.

The Underwriters may exercise the option to purchase Option ADSs at any time in whole, or from time to time in part, on or before the thirtieth day following the date of the Prospectus, by written notice from the Representatives to the Company. Such notice shall set forth the aggregate number of Option ADSs as to which the option is being exercised and the date and time when the Option ADSs are to be delivered and paid for, which may be the same date and time as the Closing Date (as hereinafter defined) but shall not be earlier than the Closing Date nor later than the tenth full business day (as hereinafter defined) after the date of such notice (unless such time and date are postponed in accordance with the provisions of Section 10 hereof). Any such notice shall be given at least two business days prior to the date and time of delivery specified therein.

(b) The Company understands that the Underwriters intend to make a public offering of the ADSs, and initially to offer the Offered ADSs on the terms set forth in the Pricing Disclosure Package. The Company acknowledges and agrees that the Underwriters may offer and sell Offered ADSs to or through any affiliate of an Underwriter.

(c) Payment for the Offered ADSs shall be made by wire transfer in immediately available funds to the account specified by the Company to the Representatives, in the case of the Underwritten ADSs, at the offices of Davis Polk & Wardwell LLP, 450 Lexington Avenue, New York, NY 10017 at 10:00 A.M. New York City time on [●], 2018, or at such other time or place on the same or such other date, not later than the fifth business day thereafter, as the Representatives and the Company may agree upon in writing or, in the case of the Option ADSs, on the date and at the time and place specified by the Representatives in the written notice of the Underwriters' election to purchase such Option ADSs. The time and date of such payment for the Underwritten ADSs is referred to herein as the "Closing Date," and the time and date for such payment for the Option ADSs, if other than the Closing Date, is herein referred to as the "Additional Closing Date."

Payment for the Offered ADSs to be purchased on the Closing Date or the Additional Closing Date, as the case may be, shall be made against delivery to the Representatives for the respective accounts of the several Underwriters of the Offered ADSs to be purchased on such date or the Additional Closing Date, as the case may be, with any stamp duties, stamp duty reserve tax or other issuance or transfer taxes payable in connection with the sale of such Offered ADSs duly paid by the Company. Delivery of the Offered ADSs shall be made through the facilities of The Depository Trust Company ("DTC") unless the Representatives shall otherwise instruct. The certificates for the Offered ADSs will be made available for inspection and packaging by the Representatives at the office of DTC or its designated custodian not later than 1:00 P.M., New York City time, on the business day prior to the Closing Date or the Additional Closing Date, as the case may be.

(d) The Company acknowledges and agrees that the Representatives and the other Underwriters are acting solely in the capacity of an arm's length contractual counterparty to the Company with respect to the offering of the Offered ADSs contemplated hereby (including in connection with determining the terms of the offering) and not as a financial advisor or a fiduciary to, or an agent of, the Company or any other person. Additionally, neither the Representatives nor any other Underwriter is advising the Company or any other person as to any legal, tax, investment, accounting or regulatory matters in any jurisdiction. The Company shall consult with its own advisors concerning such matters and shall be responsible for making its own independent investigation and appraisal of the transactions contemplated hereby, and neither the Representatives nor the other Underwriters shall have any responsibility or liability to the Company with respect thereto. Any review by the Representatives and the other Underwriters of the Company, the transactions contemplated hereby or other matters relating to such transactions will be performed solely for the benefit of the Underwriters and shall not be on behalf of the Company.

3. Representations and Warranties of the Company. The Company represents and warrants to each Underwriter that:

(a) *Preliminary Prospectus.* No order preventing or suspending the use of any Preliminary Prospectus has been issued by the Commission, and each Preliminary Prospectus included in the Pricing Disclosure Package, at the time of filing thereof, complied in all material respects with the Securities Act, and no Preliminary Prospectus, at the time of filing thereof, contained any untrue statement of a material fact or omitted to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation or warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in any Preliminary Prospectus, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(b) *Pricing Disclosure Package*. The Pricing Disclosure Package as of the Applicable Time did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation or warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in such Pricing Disclosure Package, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof. No statement of material fact included in the Prospectus has been omitted from the Pricing Disclosure Package and no statement of material fact included in the Pricing Disclosure Package that is required to be included in the Prospectus has been omitted therefrom.

(c) *Issuer Free Writing Prospectus.* Other than the Registration Statement, the Preliminary Prospectus and the Prospectus, the Company (including its agents and representatives, other than the Underwriters in their capacity as such) has not prepared, made, used, authorized, approved or referred to and will not prepare, make, use, authorize, approve or refer to any "written communication" (as defined in Rule 405 under the Securities Act) that constitutes an offer to sell or solicitation of an offer to buy the Offered ADSs (each such communication by the Company or its agents and representatives (other than a communication referred to in clause (i) below) an "Issuer Free Writing Prospectus") other than (i) any document not constituting a prospectus pursuant to Section 2(a)(10)(a) of the Securities Act or Rule 134 under the Securities Act or (ii) the documents listed on Annex A hereto, each electronic road show and any other written communications approved in writing in advance by the Representatives. Each such Issuer Free Writing Prospectus complies in all material respects with the Securities Act, has been or will be (within the time period specified in Rule 433) filed in accordance with the Securities Act (to the extent required thereby) and does not conflict with the

information contained in the Registration Statement or the Pricing Disclosure Package, and, when taken together with the Preliminary Prospectus accompanying, or delivered prior to delivery of, such Issuer Free Writing Prospectus, did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation or warranty with respect to any statements or omissions made in each such Issuer Free Writing Prospectus or Preliminary Prospectus in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in such Issuer Free Writing Prospectus or Preliminary Prospectus, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(d) *Emerging Growth Company*. From the time of initial confidential submission of the Registration Statement to the Commission (or, if earlier, the first date on which the Company engaged directly or through any person authorized to act on its behalf in any Testing-the-Waters Communication) through the date hereof, the Company has been and is an "emerging growth company," as defined in Section 2(a) of the Securities Act (an "Emerging Growth Company"). "Testing-the-Waters Communication" means any oral or written communication with potential investors undertaken in reliance on Section 5(d) of the Securities Act.

(e) *Testing-the-Waters Materials.* The Company (i) has not alone engaged in any Testing-the-Waters Communications other than Testing-the-Waters Communications with the consent of the Representatives with entities that are qualified institutional buyers within the meaning of Rule 144A under the Securities Act or institutions that are accredited investors within the meaning of Rule 501 under the Securities Act and (ii) has not authorized anyone other than the Representatives to engage in Testing-the-Waters Communications. The Company reconfirms that the Representatives have been authorized to act on its behalf in undertaking Testing-the-Waters Communications by virtue of a writing substantially in the form of Exhibit A hereto. The Company has not distributed or approved for distribution any Written Testing-the-Waters Communications other than those listed on Annex B hereto. "Written Testing-the-Waters Communication" means any Testing-the-Waters Communication that is a written communication within the meaning of Rule 405 under the Securities Act. Any individual Written Testing-the-Waters Communication does not conflict with the information contained in the Registration Statement or the Pricing Disclosure Package, complied in all material respects with the applicable requirements of the Securities Act, and when taken together with the Pricing Disclosure Package as of the Applicable Time, did not, and as of the Closing Date and as of the Additional Closing Date, as the case may be, will not, contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading.

(f) *Registration Statement and Prospectus.* The Registration Statement has been declared effective by the Commission. No order suspending the effectiveness of the Registration Statement has been issued by the Commission, and no proceeding for that purpose or pursuant to Section 8A of the Securities Act against the Company or related to the offering of the Offered ADSs has been initiated or, to the knowledge of the Company, threatened by the Commission; as of the applicable effective date of the Registration Statement and any post-effective amendment thereto, the Registration Statement and any such post-effective amendment complied and will comply in all material respects with the applicable requirements of the Securities Act, and did not and will not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein not misleading; and as of the date of the Prospectus and any amendment or supplement thereto and as of the Closing Date and as of the Additional Closing Date, as the case may be, the Prospectus will comply in all material respects with the applicable requirements of the Securities Act and will not contain any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances under which they were made, not misleading; provided that the Company makes no representation or warranty with respect to any statements or omissions made in reliance upon and in conformity with information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in the Registration Statement and the Prospectus and any amendment or supplement thereto, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in Section 7(b) hereof.

(g) *Form F-6.* A registration statement on Form F-6 (File No. 333-227905), and any amendments thereto, in respect of the Offered ADSs has been filed with the Commission; such registration statement in the form heretofore delivered to the Representatives and has been declared effective by the Commission; no stop order suspending the effectiveness of such registration statement has been issued and, to the knowledge of the Company, no proceeding for that purpose has been initiated or threatened by the Commission (the various parts of such registration statement, including all exhibits thereto, each as amended at the time such part of the registration statement became effective, being hereinafter called the "ADS Registration Statement"); as of the applicable effective date of the ADS Registration Statement and any post-effective amendment thereto, the ADS Registration Statement and any such post-effective amendment complied and will comply in all material respects with the applicable requirements of the Securities Act, and did not and will not contain any untrue statement of a material fact or omit to state a material fact required to be stated therein or necessary in order to make the statements therein not misleading.

(h) *Financial Statements.* The financial statements (including the related notes thereto) of the Company and its consolidated subsidiaries included in the Registration Statement, the Pricing Disclosure Package and the Prospectus comply in all material respects with the applicable requirements of the Securities Act and present fairly the financial position of the Company and its consolidated subsidiaries as of the dates indicated and the results of their operations and the changes in their cash flows for the periods specified; such financial statements have been prepared in conformity with

generally accepted accounting principles ("GAAP") in the United States applied on a consistent basis throughout the periods covered thereby, except in the case of unaudited financial statements, which are subject to normal year-end adjustments and do not contain footnotes as permitted by the applicable rules of the Commission, and any supporting schedules included in the Registration Statement present fairly in all material respects the information required to be stated therein; and the other financial information included in the Registration Statement, the Pricing Disclosure Package and the Prospectus has been derived from the accounting records of the Company and its consolidated subsidiaries and presents fairly in all material respects the information shown thereby; all disclosures included in the Registration Statement, the Pricing Disclosure Package and the Prospectus regarding "non-GAAP financial measures" (as such term is defined by the rules and regulations of Commission) comply with Regulation G of the Exchange Act and Item 10 of Regulation S-K of the Securities Act, to the extent applicable.

(i) *No Material Adverse Change.* Since the date of the most recent financial statements of the Company included in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (i) there has not been any change in the capital stock (other than the issuance of Ordinary Shares upon exercise of stock options and warrants described as outstanding in, and the grant of options and awards under existing equity incentive plans described in, the Registration Statement, the Pricing Disclosure Package and the Prospectus), short-term debt or long-term debt of the Company or any of its subsidiaries, or any dividend or distribution of any kind declared, set aside for payment, paid or made by the Company on any class of capital stock, or any material adverse change, or any development involving a prospective material adverse change, in or affecting the business, properties, management, financial position, stockholders' equity, results of operations or prospects of the Company and its subsidiaries taken as a whole; (ii) neither the Company nor any of its subsidiaries has entered into any transaction or agreement (whether or not in the ordinary course of business) that is material to the Company and its subsidiaries taken as a whole or incurred any liability or obligation, direct or contingent, that is material to the Company and its subsidiaries taken as a whole; and (iii) neither the Company nor any of its subsidiaries has sustained any loss or interference with its business that is material to the Company and its subsidiaries taken as a whole and that is either from fire, explosion, flood or other calamity, whether or not covered by insurance, or from any labor disturbance or dispute or any action, order or decree of any court or arbitrator or governmental or regulatory authority, except in each case as otherwise disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(j) *Organization and Good Standing.* The Company and each of its subsidiaries have been duly incorporated and are validly existing and in good standing under the laws of their respective jurisdictions of incorporated, are duly qualified to do business and are in good standing in each jurisdiction in which their respective ownership or lease of property or the conduct of their respective businesses requires such qualification, and have all power and authority necessary to own or hold their respective properties and to conduct the businesses in which they are engaged, except where the failure to be so qualified or in good standing or have such power or authority would not,

individually or in the aggregate, reasonably be expected to have a material adverse effect on the business, properties, management, financial position, stockholders' equity, results of operations or prospects of the Company and its subsidiaries taken as a whole or on the performance by the Company of its obligations under this Agreement (a "Material Adverse Effect"). The Company does not own or control, directly or indirectly, any corporation, association or other entity other than the subsidiaries listed in Exhibit 21 to the Registration Statement.

(k) *Capitalization.* The Company has an authorized share capital as set forth in the Registration Statement, the Pricing Disclosure Package and the Prospectus under the heading "Capitalization"; all the outstanding shares of capital stock of the Company have been duly and validly authorized and issued and are fully paid and non-assessable and are not subject to any pre-emptive or similar rights (save for those granted under applicable law); except as described in or expressly contemplated by the Registration Statement, the Pricing Disclosure Package and the Prospectus, there are no outstanding rights (including, without limitation, pre-emptive rights (save for those granted under applicable law)), warrants or options to acquire, or instruments convertible into or exchangeable for, any shares of capital stock or other equity interest in the Company or any of its subsidiaries, or any contract, commitment, agreement, understanding or arrangement of any kind relating to the issuance of any capital stock of the Company or any such subsidiary, any such convertible or exchangeable securities or any such rights, warrants or options; the capital stock of the Company conforms in all material respects to the description thereof contained in the Registration Statement, the Pricing Disclosure Package and the Prospectus; and all the outstanding shares of capital stock or other equity interests of each subsidiary owned, directly or indirectly, by the Company have been duly and validly authorized and issued, are fully paid and non-assessable and are owned directly or indirectly by the Company, free and clear of any lien, charge, encumbrance, security interest, restriction on voting or transfer or any other claim of any third party.

(l) *Stock Options.* With respect to the stock options (the "Stock Options") granted pursuant to the stock-based compensation plans of the Company and its subsidiaries (the "Company Stock Plans"), (i) each Stock Option intended to qualify as an "incentive stock option" under Section 422 of the Code so qualifies, (ii) each grant of a Stock Option was duly authorized no later than the date on which the grant of such Stock Option was by its terms to be effective by all necessary corporate action, including, as applicable, approval by the board of directors of the Company (or a duly constituted and authorized committee thereof) and any required stockholder approval by the necessary number of votes or written consents, and the award agreement governing such grant (if any) was duly executed and delivered by each party thereto, (iii) each such grant was made in all material respects in accordance with the terms of the Company Stock Plans and all other applicable laws and regulatory rules or requirements, and (iv) each such grant was properly accounted for in accordance with GAAP in the financial statements (including the related notes) of the Company. The Company has not knowingly granted, and there is not currently and has been no policy or practice of the Company of coordinating the grant of Stock Options with, the release or other public announcement of material information regarding the Company or its subsidiaries or their results of operations or prospects.

(m) *Due Authorization.* The Company has full right, power and authority to execute and deliver this Agreement and the Deposit Agreement (collectively, the "Transaction Documents") and to perform its obligations hereunder and thereunder; and all action required to be taken for the due and proper authorization, execution and delivery by it of this Agreement and each of the Transaction Documents and the consummation by it of the transactions contemplated hereby and thereby has been duly and validly taken.

(n) *Underwriting Agreement.* This Agreement has been duly authorized, executed and delivered by the Company.

(o) *The Shares.* The Shares to be issued and sold by the Company hereunder have been duly authorized by the Company and, when issued and delivered and paid for as provided herein, will be duly and validly issued, will be fully paid and nonassessable and will conform in all material respects to the descriptions thereof in the Registration Statement, the Pricing Disclosure Package and the Prospectus; and the issuance of the Shares is not subject to any preemptive or similar rights (save for those granted under applicable law). The Shares may be freely deposited by the Company with the Depositary against issuance of the Offered ADSs; the Offered ADSs to be sold by the Company, when issued and delivered against payment thereof, will be freely transferable by the Company to or for the account of the several Underwriters and (to the extent described in the Prospectus) the initial purchasers thereof; and there are no restrictions on subsequent transfers of the Offered ADSs under the laws of England and Wales or the United States except as disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus under "Description of Share Capital and Articles of Association," "Description of American Depositary Shares" and "Shares and ADSs Eligible for Future Sale."

(p) *Deposit Agreement*. The Deposit Agreement has been duly authorized by the Company and, when duly executed and delivered in accordance with its terms by each of the parties thereto, will constitute a valid and legally binding agreement of the Company enforceable against the Company in accordance with its terms, except as enforceability may be limited by applicable bankruptcy, insolvency, reorganization or similar laws affecting the enforcement of creditors' rights generally or by equitable principles relating to enforceability.

(q) *Description of the Transaction Documents.* Each Transaction Document conforms in all material respects to the description thereof contained in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(r) *No Violation or Default.* Neither the Company nor any of its subsidiaries is (i) in violation of its charter or by-laws or similar organizational documents; (ii) in default, and no event has occurred that, with notice or lapse of time or both, would constitute such a default, in the due performance or observance of any term, covenant or condition contained in any indenture, mortgage, deed of trust, loan agreement or other agreement or instrument to which the Company or any of its subsidiaries is a party or by which the Company or any of its subsidiaries is bound or to which any property or asset of the

Company or any of its subsidiaries is subject; or (iii) in violation of any law or statute or any judgment, order, rule or regulation of any court or arbitrator or governmental or regulatory authority, except, in the case of clauses (ii) and (iii) above, for any such default or violation that would not, individually or in the aggregate, have a Material Adverse Effect.

(s) *No Conflicts.* The execution, delivery and performance by the Company of each of the Transaction Documents, the issuance and sale of the Offered ADSs and the consummation of the transactions contemplated by the Transaction Documents or the Pricing Disclosure Package and the Prospectus will not (i) conflict with or result in a breach or violation of any of the terms or provisions of, or constitute a default under, result in the termination, modification or acceleration of, or result in the creation or imposition of any lien, charge or encumbrance upon any property, right or asset of the Company or any of its subsidiaries pursuant to, any indenture, mortgage, deed of trust, loan agreement or other agreement or instrument to which the Company or any of its subsidiaries is a party or by which the Company or any of its subsidiaries is bound or to which any property, right or asset of the Company or any of its subsidiaries is subject, (ii) result in any violation of the provisions of the charter or by-laws or similar organizational documents of the Company or any of its subsidiaries or (iii) result in the violation of any law or statute or any judgment, order, rule or regulation of any court or arbitrator or governmental or regulatory authority, except, in the case of clauses (i) and (iii) above, for any such conflict, breach, violation, default, lien, charge or encumbrance that would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect.

(t) *No Consents Required.* No consent, approval, authorization, order, registration or qualification of or with any court or arbitrator or governmental or regulatory authority is required for the execution, delivery and performance by the Company of each of the Transaction Documents, the issuance and sale of the Offered ADSs and the consummation of the transactions contemplated by the Transaction Documents, except for the registration of the ADSs under the Securities Act and such consents, approvals, authorizations, orders and registrations or qualifications as may be required by the Financial Industry Regulatory Authority, Inc. ("FINRA"), the Nasdaq Global Market or under applicable state securities laws in connection with the purchase and distribution of the Offered ADSs by the Underwriters.

(u) *Legal Proceedings.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, there are no legal, governmental or regulatory investigations, actions, demands, claims, suits, arbitrations, inquiries or proceedings ("Actions") current or pending or, to the knowledge of the Company, threatened Actions to which the Company or any of its subsidiaries is or may be a party or to which any property of the Company or any of its subsidiaries is or may be the subject that, individually or in the aggregate, if determined adversely to the Company or any of its subsidiaries, could reasonably be expected to have a Material Adverse Effect; no such Actions are threatened or, to the knowledge of the Company, contemplated by any governmental or regulatory authority or threatened by others; and (i) there are no current or pending Actions that are required under the Securities Act to be described in the Registration Statement, the Pricing Disclosure Package or the Prospectus that are not

so described in the Registration Statement, the Pricing Disclosure Package and the Prospectus and (ii) there are no statutes, regulations or contracts or other documents that are required under the Securities Act to be filed as exhibits to the Registration Statement or described in the Registration Statement, the Pricing Disclosure Package or the Prospectus that are not so filed as exhibits to the Registration Statement or described in the Registration Statement, the Pricing Disclosure Package and the Prospectus.

(v) *Independent Accountants*. PricewaterhouseCoopers LLP, who have certified certain financial statements of the Company and its subsidiaries, is an independent registered public accounting firm with respect to the Company and its subsidiaries within the applicable rules and regulations adopted by the Commission and the Public Company Accounting Oversight Board (United States) and as required by the Securities Act.

(w) *Title to Real and Personal Property*. The Company and its subsidiaries have good and marketable title in fee simple to, or have valid rights to lease or otherwise use, all items of real and personal property that are material to the respective businesses of the Company and its subsidiaries, in each case free and clear of all liens, encumbrances, claims and defects and imperfections of title except those that (i) do not materially interfere with the use made and proposed to be made of such property by the Company and its subsidiaries or (ii) could not reasonably be expected, individually or in the aggregate, to have a Material Adverse Effect.

(x) *Intellectual Property.* Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus or as could not reasonably be expected, individually or in the aggregate, to have a Material Adverse Effect, (i) the Company and its subsidiaries own or possess adequate rights to use all patents, trademarks, service marks, trade names, domain names and other source indicators, copyrights and copyrightable works, licenses and know-how, trade secrets and other unpatented and/or unpatentable proprietary or confidential information, systems or procedures, and all other worldwide intellectual property, industrial property and proprietary rights (including all registrations and applications for registration of, and all goodwill associated with, any of the foregoing) (collectively, "Intellectual Property") used or held for use in, or otherwise necessary for, the conduct of their respective businesses as currently conducted and as proposed to be conducted in the Registration Statement, the Pricing Disclosure Package and the Prospectus; provided that this clause (i) shall not be construed as a representation or warranty of non-infringement of Intellectual Property; (ii) the Company and its subsidiaries' conduct of their respective businesses has not conflicted with, infringed, misappropriated or otherwise violated any Intellectual Property rights other than patent rights of any third party and, to knowledge of the Company, the Company and its subsidiaries' conduct of their respective business has not infringed or otherwise violated any patent of any third party (it being understood that the foregoing representation and warranty is made without giving effect to any exemption under applicable law to which the Company may be entitled (e.g., 35 U.S.C. Section 271(e)(1)); (iii) the Company and its subsidiaries have not received any written notice of any claim of infringement, misappropriation or other violation of, or conflict with, any Intellectual Property of any third party, or any written notice challenging the ownership,

validity, enforceability or scope of any Intellectual Property of the Company or any of its subsidiaries; (iv) to the knowledge of the Company, the Intellectual Property of the Company and its subsidiaries has not been in conflict with, infringed, misappropriated or otherwise violated by any third party; (v) to the knowledge of the Company, all Intellectual Property of the Company and its subsidiaries is valid and enforceable; and (vi) the Company and its subsidiaries have taken reasonable steps in accordance with normal industry practice to maintain the confidentiality of all Intellectual Property of the Company and its subsidiaries the value of which to the Company or any of its subsidiaries is contingent upon maintaining the confidentiality thereof and no such Intellectual Property has been disclosed other than to employees, representatives and agents of the Company or any of its subsidiaries, all of whom are bound by written confidentiality agreements.

(y) *No Undisclosed Relationships*. No relationship, direct or indirect, exists between or among the Company or any of its subsidiaries, on the one hand, and the directors, officers, stockholders, customers, suppliers or other affiliates of the Company or any of its subsidiaries, on the other, that is required by the Securities Act to be described in each of the Registration Statement and the Prospectus and that is not so described in such documents and in the Pricing Disclosure Package.

(z) *Investment Company Act*. The Company is not and, after giving effect to the offering and sale of the Offered ADSs and the application of the proceeds thereof as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, will not be required to register as an "investment company" or an entity "controlled" by an "investment company" within the meaning of the Investment Company Act of 1940, as amended, and the rules and regulations of the Commission thereunder (collectively, the "Investment Company Act").

(aa) *Taxes.* The Company and its subsidiaries have paid all federal, state, local and foreign taxes and filed all tax returns required to be paid or filed through the date hereof; and except as otherwise disclosed in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus, there is no tax deficiency that has been, or could reasonably be expected to be, asserted against the Company or any of its subsidiaries or any of their respective properties or assets that could reasonably be expected to have a Material Adverse Effect.

(bb) *Licenses and Permits.* The Company and its subsidiaries possess all licenses, sub-licenses, certificates, permits and other authorizations issued by, and have made all declarations and filings with, the appropriate federal, state, local or foreign governmental or regulatory authorities that are necessary for the ownership or lease of their respective properties or the conduct of their respective businesses as described in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus, except where the failure to possess or make the same would not, individually or in the aggregate, have a Material Adverse Effect; and except as described in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus, neither the Company nor any of its subsidiaries has received notice of any revocation or modification of any such license, sub-license, certificate, permit or authorization or has

any reason to believe that any such license, sub-license, certificate, permit or authorization will not be renewed in the ordinary course, except where the failure to pay or file or where such revocation, modification or nonrenewal could not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect.

(cc) *No Labor Disputes.* No labor disturbance by or dispute with employees of the Company or any of its subsidiaries exists or, to the knowledge of the Company, is contemplated or threatened, and the Company is not aware of any existing or imminent labor disturbance by, or dispute with, the employees of any of its or its subsidiaries' principal suppliers, contractors or customers, except as would not have a Material Adverse Effect. Neither the Company nor any of its subsidiaries has received any notice of cancellation or termination with respect to any collective bargaining agreement to which it is a party.

(dd) *Certain Environmental Matters*. (i) The Company and its subsidiaries (x) are in compliance with all, and have not violated any, applicable federal, state, local and foreign laws (including common law), rules, regulations, requirements, decisions, judgments, decrees, orders and other legally enforceable requirements relating to pollution or the protection of human health or safety, the environment, natural resources, hazardous or toxic substances or wastes, pollutants or contaminants (collectively, "Environmental Laws"); (y) have received and are in compliance with all, and have not violated any, permits, licenses, certificates or other authorizations or approvals required of them under any Environmental Laws to conduct their respective businesses; and (z) have not received notice of any actual or potential liability or obligation under or relating to, or any actual or potential violation of, any Environmental Laws, including for the investigation or remediation of any disposal or release of hazardous or toxic substances or wastes, pollutants or contaminants, and have no knowledge of any event or condition that would reasonably be expected to result in any such notice, and (ii) there are no costs or liabilities associated with Environmental Laws of or relating to the Company or its subsidiaries, except in the case of each of (i) and (ii) above, for any such matter as would not, individually or in the aggregate, reasonably be expected to have a Material Adverse Effect; and (iii) except as described in each of the Pricing Disclosure Package and the Prospectus, (x) there is no proceeding that is pending, or that is known to be contemplated, against the Company or any of its subsidiaries under any Environmental Laws in which a governmental entity is also a party, other than such proceeding regarding which it is reasonably believed no monetary sanctions of $100,000 or more will be imposed, (y) the Company and its subsidiaries are not aware of any facts or issues regarding compliance with Environmental Laws, or liabilities or other obligations under Environmental Laws or concerning hazardous or toxic substances or wastes, pollutants or contaminants, that could reasonably be expected to have a material effect on the capital expenditures, earnings or competitive position of the Company and its subsidiaries, and (z) none of the Company or its subsidiaries anticipates material capital expenditures relating to any Environmental Laws.

(ee) *Compliance with ERISA*. (i) Each employee benefit plan, within the meaning of Section 3(3) of the Employee Retirement Income Security Act of 1974, as amended ("ERISA"), for which the Company or any member of its "Controlled Group"

(defined as any entity, whether or not incorporated, that is under common control with the Company within the meaning of Section 4001(a)(14) of ERISA or any entity that would be regarded as a single employer with the Company under Section 414(b),(c),(m) or (o) of the Internal Revenue Code of 1986, as amended (the "Code")) would have any liability (each, a "Plan") has been maintained in compliance with its terms and the requirements of any applicable statutes, orders, rules and regulations, including but not limited to ERISA and the Code; (ii) no prohibited transaction, within the meaning of Section 406 of ERISA or Section 4975 of the Code, has occurred with respect to any Plan, excluding transactions effected pursuant to a statutory or administrative exemption; (iii) for each Plan that is subject to the funding rules of Section 412 of the Code or Section 302 of ERISA, no Plan has failed (whether or not waived), or is reasonably expected to fail, to satisfy the minimum funding standards (within the meaning of Section 302 of ERISA or Section 412 of the Code) applicable to such Plan; (iv) no Plan is, or is reasonably expected to be, in "at risk status" (within the meaning of Section 303(i) of ERISA) and no Plan that is a "multiemployer plan" within the meaning of Section 4001(a)(3) of ERISA is in "endangered status" or "critical status" (within the meaning of Sections 304 and 305 of ERISA) (v) the fair market value of the assets of each Plan exceeds the present value of all benefits accrued under such Plan (determined based on those assumptions used to fund such Plan); (vi) no "reportable event" (within the meaning of Section 4043(c) of ERISA and the regulations promulgated thereunder) has occurred or is reasonably expected to occur; (vii) each Plan that is intended to be qualified under Section 401(a) of the Code is so qualified, and nothing has occurred, whether by action or by failure to act, which would cause the loss of such qualification; (viii) neither the Company nor any member of the Controlled Group has incurred, nor reasonably expects to incur, any liability under Title IV of ERISA (other than contributions to the Plan or premiums to the Pension Benefit Guarantee Corporation, in the ordinary course and without default) in respect of a Plan (including a "multiemployer plan" within the meaning of Section 4001(a)(3) of ERISA); and (ix) none of the following events has occurred or is reasonably likely to occur: (A) a material increase in the aggregate amount of contributions required to be made to all Plans by the Company or its Controlled Group affiliates in the current fiscal year of the Company and its Controlled Group affiliates compared to the amount of such contributions made in the Company's and its Controlled Group affiliates' most recently completed fiscal year; or (B) a material increase in the Company and its subsidiaries' "accumulated post-retirement benefit obligations" (within the meaning of Accounting Standards Codification Topic 715-60) compared to the amount of such obligations in the Company and its subsidiaries' most recently completed fiscal year, except in each case with respect to the events or conditions set forth in (i) through (ix) hereof, as would not, individually or in the aggregate, have a Material Adverse Effect.

(ff) *Disclosure Controls*. The Company and its subsidiaries maintain an effective system of "disclosure controls and procedures" (as defined in Rule 13a-15(e) of the Exchange Act) that complies with the requirements of the Exchange Act and that has been designed to ensure that information required to be disclosed by the Company in reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Commission's rules and forms, including controls and procedures designed to ensure that such information is

accumulated and communicated to the Company's management as appropriate to allow timely decisions regarding required disclosure. The Company and its subsidiaries have carried out evaluations of the effectiveness of their disclosure controls and procedures as required by Rule 13a-15 of the Exchange Act.

(gg) *Accounting Controls.* The Company and its subsidiaries have established systems of "internal control over financial reporting" (as defined in Rule 13a-15(f) of the Exchange Act) that comply with the requirements of the Exchange Act and have been designed by, or under the supervision of, their respective principal executive and principal financial officers, or persons performing similar functions, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with GAAP. The Company and its subsidiaries maintain internal accounting controls sufficient to provide reasonable assurance that (i) transactions are executed in accordance with management's general or specific authorizations; (ii) transactions are recorded as necessary to permit preparation of financial statements in conformity with GAAP and to maintain asset accountability; (iii) access to assets is permitted only in accordance with management's general or specific authorization; and (iv) the recorded accountability for assets is compared with the existing assets at reasonable intervals and appropriate action is taken with respect to any differences. Based on the Company's most recent evaluation of its internal controls over financial reporting pursuant to Rule 13a-15(c) of the Exchange Act, except as disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus, there are no material weaknesses in the Company's internal controls. The Company's auditors and the Audit Committee of the Board of Directors of the Company have been advised of: (i) all significant deficiencies and material weaknesses in the design or operation of internal controls over financial reporting which have adversely affected or are reasonably likely to adversely affect the Company's ability to record, process, summarize and report financial information; and (ii) any fraud, whether or not material, that involves management or other employees who have a significant role in the Company's internal controls over financial reporting.

(hh) *Insurance.* The Company and its subsidiaries have insurance covering their respective properties, operations, personnel and businesses, including business interruption insurance, which insurance is in amounts and insures against such losses and risks which the Company believes are adequate to protect the Company and its subsidiaries and their respective businesses; and neither the Company nor any of its subsidiaries has (i) received notice from any insurer or agent of such insurer that capital improvements or other expenditures are required or necessary to be made in order to continue such insurance or (ii) any reason to believe that it will not be able to renew its existing insurance coverage as and when such coverage expires or to obtain similar coverage at reasonable cost from similar insurers as may be necessary to continue its business.

(ii) *Cybersecurity.* (i)(x) Except as disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus, to the Company's knowledge, there has been no security breach or other compromise of or relating to any of the Company's or any of its subsidiaries' information technology and computer systems, networks, hardware, software, data (including the data of their respective customers, employees, suppliers, vendors and any third party data maintained by or on behalf of them), equipment or

technology (collectively, "IT Systems and Data") which could have a Material Adverse Effect and (y) the Company and its subsidiaries have not been notified of, and have no knowledge of any event or condition that would reasonably be expected to result in, any security breach or other compromise to their IT Systems and Data; (ii) the Company and its subsidiaries are presently in compliance with all applicable laws or statutes and all judgments, orders, rules and regulations of any court or arbitrator or governmental or regulatory authority, internal policies and contractual obligations relating to the privacy and security of IT Systems and Data and to the protection of such IT Systems and Data from unauthorized use, access, misappropriation or modification, except as would not, in the case of this clause (ii), individually or in the aggregate, have a Material Adverse Effect; and (iii) the Company and its subsidiaries have implemented backup and disaster recovery technology consistent with industry standards and practices.

(jj) *No Unlawful Payments.* Neither the Company nor any of its subsidiaries nor any director, officer or employee of the Company or any of its subsidiaries nor, to the knowledge of the Company, any agent, affiliate or other person associated with or acting on behalf of the Company or any of its subsidiaries has (i) used any corporate funds for any unlawful contribution, gift, entertainment or other unlawful expense relating to political activity; (ii) made or taken an act in furtherance of an offer, promise or authorization of any direct or indirect unlawful payment or benefit to any foreign or domestic government official or employee, including of any government-owned or controlled entity or of a public international organization, or any person acting in an official capacity for or on behalf of any of the foregoing, or any political party or party official or candidate for political office; (iii) violated or is in violation of any provision of the Foreign Corrupt Practices Act of 1977, as amended, or any applicable law or regulation implementing the OECD Convention on Combating Bribery of Foreign Public Officials in International Business Transactions, or committed an offence under the Bribery Act 2010 of the United Kingdom or any other applicable anti-bribery or anti-corruption law; or (iv) made, offered, agreed, requested or taken an act in furtherance of any unlawful bribe or other unlawful benefit, including, without limitation, any rebate, payoff, influence payment, kickback or other unlawful or improper payment or benefit. The Company and its subsidiaries have instituted, maintain and enforce, and will continue to maintain and enforce policies and procedures designed to promote and ensure compliance with all applicable anti-bribery and anti-corruption laws.

(kk) *Compliance with Anti-Money Laundering Laws*. The operations of the Company and its subsidiaries are and have been conducted at all times in compliance with applicable financial recordkeeping and reporting requirements, including, where applicable, those of the Currency and Foreign Transactions Reporting Act of 1970, as amended, the applicable money laundering statutes of all jurisdictions where the Company or any of its subsidiaries conducts business, the rules and regulations thereunder and any related or similar rules, regulations or guidelines issued, administered or enforced by any governmental agency (collectively, the "Anti-Money Laundering Laws") and no action, suit or proceeding by or before any court or governmental agency, authority or body or any arbitrator involving the Company or any of its subsidiaries with respect to the Anti-Money Laundering Laws is pending or, to the knowledge of the Company, threatened.

(ll) *No Conflicts with Sanctions Laws.* Neither the Company nor any of its subsidiaries, directors, officers, or employees, nor, to the knowledge of the Company, any agent, affiliate or other person associated with or acting on behalf of the Company or any of its subsidiaries is currently the subject or the target of any sanctions administered or enforced by the U.S. government, (including, without limitation, the Office of Foreign Assets Control of the U.S. Department of the Treasury ("OFAC") or the U.S. Department of State and including, without limitation, the designation as a "specially designated national" or "blocked person"), the United Nations Security Council ("UNSC"), the European Union, Her Majesty's Treasury ("HMT") or other relevant sanctions authority (collectively, "Sanctions"), nor is the Company or any of its subsidiaries located, organized or resident in a country or territory that is the subject or target of Sanctions, including, without limitation, Crimea, Cuba, Iran, North Korea, Sudan and Syria (each, a "Sanctioned Country"); and the Company will not directly or indirectly use the proceeds of the offering of the Offered ADSs hereunder, or lend, contribute or otherwise make available such proceeds to any subsidiary, joint venture partner or other person or entity (i) to fund or facilitate any activities of or business with any person that, at the time of such funding or facilitation, is the subject or target of Sanctions, (ii) to fund or facilitate any activities of or business in any Sanctioned Country or (iii) in any other manner that will result in a violation by any person (including any person participating in the transaction, whether as underwriter, advisor, investor or otherwise) of Sanctions. Since the Company's inception, the Company and its subsidiaries have not knowingly engaged in and are not now knowingly engaged in any dealings or transactions with any person that at the time of the dealing or transaction is or was the subject or the target of Sanctions or with any Sanctioned Country.

(mm) *No Restrictions on Subsidiaries*. No subsidiary of the Company is currently prohibited, directly or indirectly, under any agreement or other instrument to which it is a party or is subject, from paying any dividends to the Company, from making any other distribution on such subsidiary's capital stock or similar ownership interest, from repaying to the Company any loans or advances to such subsidiary from the Company or from transferring any of such subsidiary's properties or assets to the Company or any other subsidiary of the Company.

(nn) *No Broker's Fees.* Neither the Company nor any of its subsidiaries is a party to any contract, agreement or understanding with any person (other than this Agreement) that would give rise to a valid claim against any of them or any Underwriter for a brokerage commission, finder's fee or like payment in connection with the offering and sale of the ADSs.

(oo) *No Registration Rights*. No person has the right to require the Company or any of its subsidiaries to register any securities for sale under the Securities Act by reason of the filing of the Registration Statement with the Commission or the issuance and sale of the Offered ADSs, other than rights that have been validly waived.

(pp) *No Stabilization.* Neither the Company nor any of its subsidiaries has taken, directly or indirectly, any action designed to or that could reasonably be expected to cause or result in any stabilization or manipulation of the price of the Offered ADSs.

(qq) *Margin Rules*. Neither the issuance, sale and delivery of the Offered ADSs nor the application of the proceeds thereof by the Company as described in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus will violate Regulation T, U or X of the Board of Governors of the Federal Reserve System or any other regulation of such Board of Governors.

(rr) *Forward-Looking Statements*. No forward-looking statement (within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act) included or incorporated by reference in any of the Registration Statement, the Pricing Disclosure Package or the Prospectus has been made or reaffirmed without a reasonable basis or has been disclosed other than in good faith.

(ss) *Statistical and Market Data.* Nothing has come to the attention of the Company that has caused the Company to believe that the statistical and market-related data included in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus is not based on or derived from sources that are reliable and accurate in all material respects.

(tt) *Sarbanes-Oxley Act*. There is and has been no failure on the part of the Company or any of the Company's directors or officers, in their capacities as such, to comply with any applicable provision of the Sarbanes-Oxley Act of 2002, as amended and the rules and regulations promulgated in connection therewith (the "Sarbanes-Oxley Act"), including Section 402 related to loans and Sections 302 and 906 related to certifications.

(uu) *Status under the Securities Act*. At the time of filing the Registration Statement and any post-effective amendment thereto, at the earliest time thereafter that the Company or any offering participant made a *bona fide* offer (within the meaning of Rule 164(h)(2) under the Securities Act) of the Offered ADSs and at the date hereof, the Company was not and is not an "ineligible issuer," as defined in Rule 405 under the Securities Act.

(vv) *No Ratings*. There are (and prior to the Closing Date, will be) no debt securities or preferred stock issued or guaranteed by the Company or any of its subsidiaries that are rated by a "nationally recognized statistical rating organization", as such term is defined in Section 3(a)(62) under the Exchange Act.

(ww) *Preclinical Studies and Clinical Trials*. (i) Except as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the preclinical studies and clinical trials conducted by or, to the knowledge of the Company, on behalf of or sponsored by the Company or its subsidiaries, or in which the Company or its subsidiaries have participated, that are described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, or the results of which are referred to in

the Registration Statement, the Pricing Disclosure Package and the Prospectus, as applicable, were, and if still pending are, being conducted in all material respects in accordance with all applicable statutes and all applicable rules and regulations of the applicable regulatory agencies to which they are subject, including the U.S. Food and Drug Administration and the European Medicines Agency (collectively, the "Regulatory Authorities") and Good Clinical Practice and Good Laboratory Practice requirements; (ii) the descriptions in the Registration Statement, the Pricing Disclosure Package and the Prospectus of the results of such studies and trials are accurate and complete descriptions in all material respects and fairly present the data derived therefrom as of the dates given for such data in the Registration Statement; (iii) the Company has no knowledge of any other studies or trials conducted by or on behalf of the Company not described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the results of which are inconsistent with or call into question the results described or referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus; (iv) the Company and its subsidiaries have operated at all times and are currently in compliance in all respects with all applicable statutes, rules and regulations of the Regulatory Authorities, except that where such non-compliance would not, individually or in the aggregate, have a Material Adverse Effect; (v) the Company has provided the Underwriters with all substantive written notices, correspondence and summaries of all other communications from the Regulatory Authorities; and (vi) neither the Company nor any of its subsidiaries have received any written notices, correspondence or other communications from the Regulatory Authorities or any other governmental agency requiring or threatening the termination, material modification or suspension of any preclinical studies or clinical trials that are described in the Registration Statement, the Pricing Disclosure Package and the Prospectus or the results of which are referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus, other than ordinary course communications with respect to modifications in connection with the design and implementation of such studies or trials, and, to the Company's knowledge, there are no reasonable grounds for the same.

(xx) *Regulatory Filings*. The Company has not failed to file with the Regulatory Authorities any required filing, declaration, listing, registration, report or submission with respect to the Company's product candidates that are described or referred to in the Registration Statement, the Pricing Disclosure Package and the Prospectus; all such filings, declarations, listings, registrations, reports or submissions, as applicable, were in material compliance with applicable laws when filed; and no material deficiencies regarding compliance with applicable law have been asserted by any applicable regulatory authority with respect to any such filings, declarations, listings, registrations, reports or submissions.

(yy) *Directed ADS Program.* The Company represents and warrants that (i) the Registration Statement, the Pricing Disclosure Package and the Prospectus, any Preliminary Prospectus and any Issuer Free Writing Prospectuses comply in all material respects, and any further amendments or supplements thereto will comply in all material respects, with any applicable laws or regulations of foreign jurisdictions in which the Pricing Disclosure Package, the Prospectus, any Preliminary Prospectus and any Issuer Free Writing Prospectus, as amended or supplemented, if applicable, are distributed in

connection with the Directed ADS Program, and that (ii) no authorization, approval, consent, license, order, registration or qualification of or with any government, governmental instrumentality or court, other than such as have been obtained, is necessary under the securities laws and regulations of foreign jurisdictions in which the Directed ADSs are offered outside the United States. The Company has not offered, or caused the underwriters to offer, ADSs to any person pursuant to the Directed ADS Program with the specific intent to unlawfully influence (i) a customer or supplier of the Company to alter the customer or supplier's level or type of business with the Company, or (ii) a trade journalist or publication to write or publish favorable information about the Company or its products.

(zz) *Stamp Taxes*. Except as described in the Registration Statement or the Prospectus and except for any net income, or franchise taxes imposed on the Underwriters by the United Kingdom or any political subdivision or taxing authority thereof or therein as a result of any present or former connection (other than any connection resulting from the transactions contemplated by this Agreement) between the Underwriters and the jurisdiction imposing such tax, no stamp duty, stamp duty reserve tax, documentary, issuance, transfer, capital, registration or other similar taxes or duties are payable by or on behalf of the Underwriters in the United Kingdom, the United States, or any other jurisdiction (including taxes or duties imposed by any political subdivision or taxing authority thereof) in connection with (A) the execution and delivery, performance or enforcement of this Agreement, (B) the issuance, allotment and delivery of the Shares and the Offered ADSs in the manner contemplated by this Agreement and the Prospectus, or (C) the sale and delivery by the Underwriters of the Offered ADSs as contemplated herein and in the Prospectus.

(aaa) *Taxes on Corporate Reorganization.* No Liability to tax which, individually or in the aggregate, would reasonably be expected to have a Material Adverse Effect will arise to the Company or any subsidiary as a result of the Corporate Reorganization.

(bbb) *No Immunity*. Neither the Company nor any of its subsidiaries or their properties or assets has immunity under English, U.S. federal or New York state law from any legal action, suit or proceeding, from the giving of any relief in any such legal action, suit or proceeding, from set-off or counterclaim, from the jurisdiction of any English, U.S. federal or New York state court, from service of process, attachment upon or prior to judgment, or attachment in aid of execution of judgment, or from execution of a judgment, or other legal process or proceeding for the giving of any relief or for the enforcement of a judgment, in any such court with respect to their respective obligations, liabilities or any other matter under or arising out of or in connection herewith; and, to the extent that the Company or any of its subsidiaries or any of its properties, assets or revenues may have or may hereafter become entitled to any such right of immunity in any such court in which proceedings arising out of, or relating to the transactions contemplated by the Transaction Documents, may at any time be commenced, the Company has, pursuant to Section 16(e) of this Agreement, waived, and it will waive, or will cause its subsidiaries to waive, such right to the extent permitted by law.

(ccc) *Enforcement of Foreign Judgments*. Any final judgment for a fixed or determined sum of money rendered by any U.S. federal or New York state court located in the State of New York having jurisdiction under its own laws in respect of any suit, action or proceeding against the Company based upon this Agreement would be declared enforceable against the Company by the courts of England and Wales, without reconsideration or reexamination of the merits.

(ddd) *Valid Choice of Law*. The choice of laws of the State of New York as the governing law of the Transaction Documents is a valid choice of law under the laws of England and Wales and will be honored by the courts of England and Wales, subject to the restrictions described under the caption "Service of process and enforcement of liabilities" in the Registration Statement, the Pricing Disclosure Package and the Prospectus. The Company has the power to submit, and pursuant to Section 16(b) of this Agreement, has legally, validly, effectively and irrevocably submitted, to the personal jurisdiction of each New York state and United States federal court sitting in the City of New York and has validly and irrevocably waived any objection to the laying of venue of any suit, action or proceeding brought in such court.

(eee) *Indemnification and Contribution*. The indemnification and contribution provisions set forth in Section 7 hereof do not contravene English law or public policy.

(fff) *Passive Foreign Investment Company*. Subject to the qualifications, limitations, exceptions and assumptions set forth in the Registration Statement, the Pricing Disclosure Package and the Prospectus, the Company does not expect it was treated as, for the taxable year ending December 31, 2017, a passive foreign investment company as defined in Section 1297 of the Code.

(ggg) *Dividends*. Except as disclosed in the Registration Statement, the Pricing Disclosure Package and the Prospectus, no approvals are currently required in the United Kingdom in order for the Company to pay dividends or other distributions declared by the Company to the holders of Shares. Under current laws and regulations of the United Kingdom and any political subdivision thereof, any amount payable with respect to the Shares upon liquidation of the Company or upon redemption thereof and dividends and other distributions declared and payable on the share capital of the Company may be paid by the Company in United States dollars or euros and freely transferred out of the United Kingdom, and no such payments made to the holders thereof or therein who are non-residents of the United Kingdom will be subject to income, withholding or other taxes under laws and regulations of the United Kingdom or any political subdivision or taxing authority thereof or therein and without the necessity of obtaining any governmental authorization in the United Kingdom or any political subdivision or taxing authority thereof or therein.

(hhh) *Legality*. Other than filings required to be made with the Commission, the legality, validity, enforceability or admissibility into evidence of any of the Registration Statement, the Pricing Disclosure Package, the Prospectus, this Agreement or the Offered ADSs in any jurisdiction in which the Company is organized or does business is not dependent upon such document being submitted into, filed or recorded with any court or other authority in any such jurisdiction on or before the date hereof or that any tax, imposition or charge be paid in any such jurisdiction on or in respect of any such document.

(iii) *Legal Action*. A holder of the Shares and each Underwriter are each entitled to sue as plaintiff in the court of the jurisdiction of formation and domicile of the Company for the enforcement of their respective rights under this Agreement and the Shares and such access to such courts will not be subject to any conditions which are not applicable to residents of such jurisdiction or a company incorporated in such jurisdiction except that plaintiffs not residing in England and Wales may be required to guarantee payment of a possible order for payment of costs or damages at the request of the defendant.

(jjj) *Foreign Issuer*. The Company is a "foreign private issuer" as defined in Rule 405 under the Securities Act.

4. Further Agreements of the Company. The Company covenants and agrees with each Underwriter that:

(h) *Required Filings.* The Company will file the final Prospectus with the Commission within the time periods specified by Rule 424(b) and Rule 430A, 430B or 430C under the Securities Act, will file any Issuer Free Writing Prospectus to the extent required by Rule 433 under the Securities Act; and the Company will furnish copies of the Prospectus and each Issuer Free Writing Prospectus (to the extent not previously delivered) to the Underwriters in New York City prior to 10:00 A.M., New York City time, on the business day next succeeding the date of this Agreement in such quantities as the Representatives may reasonably request.

(i) *Delivery of Copies.* The Company will deliver, without charge, (i) to the Representatives, four signed copies of the Registration Statement as originally filed and each amendment thereto, in each case including all exhibits and consents filed therewith; and (ii) to each Underwriter (A) a conformed copy of the Registration Statement as originally filed and each amendment thereto (without exhibits) and (B) during the Prospectus Delivery Period (as defined below), as many copies of the Prospectus (including all amendments and supplements thereto and each Issuer Free Writing Prospectus) as the Representatives may reasonably request. As used herein, the term "Prospectus Delivery Period" means such period of time after the first date of the public offering of the Offered ADSs as in the opinion of counsel for the Underwriters a prospectus relating to the Offered ADSs is required by law to be delivered (or required to be delivered but for Rule 172 under the Securities Act) in connection with sales of the Offered ADSs by any Underwriter or dealer.

(j) *Amendments or Supplements, Issuer Free Writing Prospectuses.* Before making, preparing, using, authorizing, approving, referring to or filing any Issuer Free Writing Prospectus, and before filing any amendment or supplement to the Registration Statement, the Pricing Disclosure Package or the Prospectus, the Company will furnish to the Representatives and counsel for the Underwriters a copy of the proposed Issuer Free Writing Prospectus, amendment or supplement for review and will not make, prepare, use, authorize, approve, refer to or file any such Issuer Free Writing Prospectus or file any such proposed amendment or supplement to which the Representatives reasonably object.

(k) *Notice to the Representatives.* The Company will advise the Representatives promptly, and confirm such advice in writing, (i) when the Registration Statement has become effective; (ii) when any amendment to the Registration Statement has been filed or becomes effective; (iii) when any supplement to the Pricing Disclosure Package, the Prospectus, any Issuer Free Writing Prospectus or any Written Testing-the-Waters Communication or any amendment to the Prospectus has been filed or distributed; (iv) of any request by the Commission for any amendment to the Registration Statement or any amendment or supplement to the Prospectus or the receipt of any comments from the Commission relating to the Registration Statement or any other request by the Commission for any additional information including, but not limited to, any request for information concerning any Testing-the-Waters Communication; (v) of the issuance by the Commission or any other governmental or regulatory authority of any order suspending the effectiveness of the Registration Statement or preventing or suspending the use of any Preliminary Prospectus, any of the Pricing Disclosure Package, the Prospectus or any Written Testing-the-Waters Communication or the initiation or threatening of any proceeding for that purpose or pursuant to Section 8A of the Securities Act; (vi) of the occurrence of any event or development within the Prospectus Delivery Period as a result of which the Prospectus, any of the Pricing Disclosure Package, any Issuer Free Writing Prospectus or any Written Testing-the-Waters Communication as then amended or supplemented would include any untrue statement of a material fact or omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Prospectus, the Pricing Disclosure Package, any such Issuer Free Writing Prospectus or any Written Testing-the-Waters Communication is delivered to a purchaser, not misleading; and (vii) of the receipt by the Company of any notice with respect to any suspension of the qualification of the Offered ADSs for offer and sale in any jurisdiction or the initiation or threatening of any proceeding for such purpose; and the Company will use its reasonable best efforts to prevent the issuance of any such order suspending the effectiveness of the Registration Statement, preventing or suspending the use of any Preliminary Prospectus, any of the Pricing Disclosure Package or the Prospectus or any Written Testing-the-Waters Communication or suspending any such qualification of the Offered ADSs and, if any such order is issued, will obtain as soon as possible the withdrawal thereof.

(l) *Ongoing Compliance.* (1) If during the Prospectus Delivery Period (i) any event or development shall occur or condition shall exist as a result of which the Prospectus as then amended or supplemented would include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Prospectus is delivered to a purchaser, not misleading or (ii) it is necessary to amend or supplement the Prospectus to comply with applicable law, the Company will promptly notify the Underwriters thereof and forthwith prepare and, subject to paragraph (c) above, file with the Commission and furnish to the Underwriters and to such dealers as the Representatives may designate such

amendments or supplements to the Prospectus as may be necessary so that the statements in the Prospectus as so amended or supplemented will not, in the light of the circumstances existing when the Prospectus is delivered to a purchaser, be misleading or so that the Prospectus will comply with applicable law and (2) if at any time prior to the Closing Date (i) any event or development shall occur or condition shall exist as a result of which the Pricing Disclosure Package as then amended or supplemented would include any untrue statement of a material fact or omit to state any material fact necessary in order to make the statements therein, in the light of the circumstances existing when the Pricing Disclosure Package is delivered to a purchaser, not misleading or (ii) it is necessary to amend or supplement the Pricing Disclosure Package to comply with applicable law, the Company will promptly notify the Underwriters thereof and forthwith prepare and, subject to paragraph (c) above, file with the Commission (to the extent required) and furnish to the Underwriters and to such dealers as the Representatives may designate such amendments or supplements to the Pricing Disclosure Package as may be necessary so that the statements in the Pricing Disclosure Package as so amended or supplemented will not, in the light of the circumstances existing when the Pricing Disclosure Package is delivered to a purchaser, be misleading or so that the Pricing Disclosure Package will comply with applicable law.

(m) *Blue Sky Compliance.* The Company will qualify the Offered ADSs for offer and sale under the securities or Blue Sky laws of such jurisdictions as the Representatives shall reasonably request and will continue such qualifications in effect so long as required for distribution of the ADSs; provided that the Company shall not be required to (i) qualify as a foreign corporation or other entity or as a dealer in securities in any such jurisdiction where it would not otherwise be required to so qualify, (ii) file any general consent to service of process in any such jurisdiction or (iii) subject itself to taxation in any such jurisdiction if it is not otherwise so subject.

(n) *Earning Statement.* The Company will make generally available to its security holders and the Representatives as soon as practicable an earning statement that satisfies the provisions of Section 11(a) of the Securities Act and Rule 158 of the Commission promulgated thereunder covering a period of at least twelve months beginning with the first fiscal quarter of the Company occurring after the "effective date" (as defined in Rule 158) of the Registration Statement; provided that the Company will be deemed to have furnished such statements to its security holders and the Representatives to the extent they are filed on the Commission's Electronic Data Gathering, Analysis, and Retrieval system ("EDGAR") or any successor system.

(o) *Clear Market.* For a period of 180 days after the date of the Prospectus (the "Restricted Period"), the Company will not (i) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, or file with, or submit to, the Commission a registration statement under the Securities Act relating to, any Ordinary Shares or ADSs or any securities convertible into or exercisable or exchangeable for Ordinary Shares or ADSs, or publicly disclose the intention to make any offer, sale, pledge, disposition, submission or filing (other than filings on Form S-8 relating to the Company Stock Plans that are disclosed in the Pricing

Disclosure Package), or (ii) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the Ordinary Shares or ADSs or any such other securities, whether any such transaction described in clause (i) or (ii) above is to be settled by delivery of Shares or such other securities, in cash or otherwise, without the prior written consent of the Representatives, other than (A) the ADSs to be sold hereunder, (B) any Ordinary Shares issued upon the conversion of the Company's preferred shares outstanding on the date of this Agreement in connection with the offering contemplated by this Agreement and as described in the Registration Statement, the Pricing Disclosure Package and the Prospectus, (C) any Ordinary Shares or ADSs of the Company issued upon the exercise of options granted under Company Stock Plans, (D) any options and other awards granted under a Company Stock Plan, or (E) up to 5% of the Company's outstanding securities issued by the Company in connection with mergers, acquisitions or commercial or strategic transactions; provided that in the case of clauses (C), (D) and (E), the recipient of such securities shall execute and deliver (if a lock-up agreement has not previously been delivered by such recipient) a lock-up agreement for the remainder of the Restricted Period in substantially the form attached as Exhibit D hereto.

If the Representatives, in their sole discretion, agree to release or waive the restrictions set forth in a lock-up letter described in Section 6(m) hereof for an officer or director of the Company and provide the Company with notice of the impending release or waiver substantially in the form of Exhibit B hereto at least three business days before the effective date of the release or waiver, the Company agrees to announce the impending release or waiver by a press release substantially in the form of Exhibit C hereto through a major news service at least two business days before the effective date of the release or waiver.

(p) *Use of Proceeds.* The Company will apply the net proceeds from the sale of the ADSs in all material respects as described in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus under the heading "Use of proceeds".

(q) *No Stabilization.* The Company will not take, directly or indirectly, any action designed to or that could reasonably be expected to cause or result in any stabilization or manipulation of the price of the Offered ADSs.

(r) *Exchange Listing.* The Company will use its reasonable best efforts to list, subject to notice of issuance, the ADSs for quotation on the Nasdaq Global Market (the "Nasdaq Market").

(s) *Reports.* For a period of two years following the date of this Agreement, the Company will furnish to the Representatives, as soon as they are available, copies of all reports or other communications (financial or other) furnished to holders of the Shares or ADSs, and copies of any reports and financial statements furnished to or filed with the Commission or any national securities exchange or automatic quotation system; provided the Company will be deemed to have furnished such reports and financial statements to the Representatives to the extent they are filed on EDGAR.

(t) *Record Retention*. The Company will, pursuant to reasonable procedures developed in good faith, retain copies of each Issuer Free Writing Prospectus that is not filed with the Commission in accordance with Rule 433 under the Securities Act.

(u) *Filings.* The Company will file with the Commission such reports as may be required by Rule 463 under the Securities Act.

(v) *Directed ADS Program.* The Company will comply with all applicable securities and other laws, rules and regulations in each jurisdiction in which the Directed ADSs are offered in connection with the Directed ADS Program.

(w) *Emerging Growth Company; Foreign Private Issuer*. The Company will promptly notify the Representatives if the Company ceases to be an Emerging Growth Company or a Foreign Private Issuer at any time prior to the later of (i) completion of the distribution of Offered ADSs within the meaning of the Securities Act and (ii) completion of the 180-day restricted period referred to in Section 4(h) hereof.

(x) *Certification Regarding Beneficial Owners*. The Company will deliver to the Representatives, on the date of execution of this Agreement, properly completed and executed Certifications Regarding Beneficial Owners of Legal Entity Customers, together with copies of identifying documentation, and the Company undertakes to provide such additional supporting documentation as the Representatives may reasonably request in connection with the verification of the foregoing certification.

(y) *Tax Indemnity*. The Company will bear, and indemnify and hold harmless the Underwriters against, any stamp duty, stamp duty reserve tax, documentary, issuance, transfer, capital, registration or other similar taxes or duties (including any interest and penalties imposed thereon) payable, in the United Kingdom, the United States, or any other jurisdiction (including taxes or duties imposed by any political subdivision or taxing authority thereof), on (A) the execution, delivery, performance or enforcement of this Agreement, (B) the issuance, allotment and delivery of the Shares and the Offered ADSs in the manner contemplated by this Agreement and the Prospectus, or (C) the sale and delivery by the Underwriters of the Offered ADSs as contemplated herein and in the Prospectus.

(z) *Gross-up*. All payments to be made by the Company hereunder shall be made without withholding or deduction for or on account of any present or future taxes, duties or governmental charges whatsoever unless the Company is compelled by law to deduct or withhold such taxes, duties or charges. In that event, the Company shall pay such additional amounts as may be necessary in order to ensure that the net amounts received after such withholding or deductions shall equal the amounts that would have been received if no withholding or deduction had been made.

(aa) *Value Added Tax*. All sums payable to the Underwriters shall be considered exclusive of any value added tax chargeable pursuant to the Value Added Tax Act 1994 (“VAT”). Where the Company is obliged to pay VAT on any amount payable hereunder to the Underwriters, the Company shall in addition to the sum payable hereunder pay an amount equal to any applicable VAT to the extent not recoverable by the Underwriters and subject to receipt of a valid VAT invoice from the Underwriters.

5. Certain Agreements of the Underwriters. Each Underwriter hereby represents and agrees that:

(h) It has not and will not use, authorize use of, refer to or participate in the planning for use of, any "free writing prospectus", as defined in Rule 405 under the Securities Act (which term includes use of any written information furnished to the Commission by the Company and not incorporated by reference into the Registration Statement and any press release issued by the Company) other than (i) a free writing prospectus that contains no "issuer information" (as defined in Rule 433(h)(2) under the Securities Act) that was not included (including through incorporation by reference) in the Preliminary Prospectus or a previously filed Issuer Free Writing Prospectus, (ii) any Issuer Free Writing Prospectus listed on Annex A or prepared pursuant to Section 3(c) or Section 4(c) above (including any electronic road show), or (iii) any free writing prospectus prepared by such Underwriter and approved by the Company in advance in writing (each such free writing prospectus referred to in clauses (i) or (iii), an "Underwriter Free Writing Prospectus").

(i) It has not and will not, without the prior written consent of the Company, use any free writing prospectus that contains the final terms of the Offered ADSs unless such terms have previously been included in a free writing prospectus filed with the Commission; *provided* that Underwriters may use a term sheet substantially in the form of Annex C hereto without the consent of the Company; *provided further* that any Underwriter using such term sheet shall notify the Company, and provide a copy of such term sheet to the Company, prior to, or substantially concurrently with, the first use of such term sheet.

(j) It is not subject to any pending proceeding under Section 8A of the Securities Act with respect to the offering (and will promptly notify the Company if any such proceeding against it is initiated during the Prospectus Delivery Period).

6. Conditions of Underwriters' Obligations. The obligation of each Underwriter to purchase the Underwritten ADSs on the Closing Date or the Option ADSs on the Additional Closing Date, as the case may be, as provided herein is subject to the performance by the Company of its covenants and other obligations hereunder and to the following additional conditions:

(a) *Registration Compliance; No Stop Order.* No order suspending the effectiveness of the Registration Statement shall be in effect, and no proceeding for such purpose or pursuant to Section 8A under the Securities Act shall be pending before or threatened by the Commission; the Prospectus and each Issuer Free Writing Prospectus shall have been timely filed with the Commission under the Securities Act (in the case of an Issuer Free Writing Prospectus, to the extent required by Rule 433 under the Securities Act) and in accordance with Section 4(a) hereof; and all requests by the Commission for additional information shall have been complied with to the reasonable satisfaction of the Representatives.

(b) *Representations and Warranties.* The representations and warranties of the Company contained herein shall be true and correct on the date hereof and on and as of the Closing Date or the Additional Closing Date, as the case may be; and the statements of the Company and its officers made in any certificates delivered pursuant to this Agreement shall be true and correct on and as of the Closing Date or the Additional Closing Date, as the case may be.

(c) *No Material Adverse Change.* No event or condition of a type described in Section 3(i) hereof shall have occurred or shall exist, which event or condition is not described in the Pricing Disclosure Package (excluding any amendment or supplement thereto) and the Prospectus (excluding any amendment or supplement thereto) and the effect of which in the judgment of the Representatives makes it impracticable or inadvisable to proceed with the offering, sale or delivery of the Offered ADSs on the Closing Date or the Additional Closing Date, as the case may be, on the terms and in the manner contemplated by this Agreement, the Pricing Disclosure Package and the Prospectus.

(d) *Officer's Certificate.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, a certificate of the chief financial officer or chief accounting officer of the Company and one additional senior executive officer of the Company who is satisfactory to the Representatives (i) confirming that such officers have carefully reviewed the Registration Statement, the Pricing Disclosure Package and the Prospectus and, to the knowledge of such officers, the representations set forth in Sections 3(b) and 3(d) hereof are true and correct, (ii) confirming that the other representations and warranties of the Company in this Agreement are true and correct and that the Company has complied with all agreements and satisfied all conditions on its part to be performed or satisfied hereunder at or prior to the Closing Date or the Additional Closing Date, as the case may be, and (iii) to the effect set forth in paragraphs (a), (b) and (c) above.

(e) *Comfort Letters.* On the date of this Agreement and on the Closing Date or the Additional Closing Date, as the case may be, PricewaterhouseCoopers LLP shall have furnished to the Representatives, at the request of the Company, letters, dated the respective dates of delivery thereof and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives, containing statements and information of the type customarily included in accountants' "comfort letters" to underwriters with respect to the financial statements and certain financial information contained in each of the Registration Statement, the Pricing Disclosure Package and the Prospectus; provided, that the letter delivered on the Closing Date or the Additional Closing Date, as the case may be, shall use a "cut-off" date no more than two business days prior to such Closing Date or such Additional Closing Date, as the case may be.

(f) *Opinion and 10b-5 Statement of U.S. Counsel for the Company.* Goodwin Procter LLP, as U.S. counsel for the Company, shall have furnished to the Representatives, at the request of the Company, their written opinion and 10b-5 statement, dated the Closing Date or the Additional Closing Date, as the case may be, and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives.

(g) *Opinion of UK Counsel for the Company.* Goodwin Procter (UK) LLP, as UK counsel for the Company, shall have furnished to the Representatives, at the request of the Company, their written opinion, dated the Closing Date or the Additional Closing Date, as the case may be, and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives.

(h) *Opinion of IP Counsel for the Company.* Clark+Elbing LLP, IP counsel for the Company, shall have furnished to the Representatives, at the request of the Company, their written opinion, dated the Closing Date or the Additional Closing Date, as the case may be, and addressed to the Underwriters, in form and substance reasonably satisfactory to the Representatives.

(i) *Opinion and 10b-5 Statement of Counsel for the Underwriters.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, an opinion and 10b-5 statement, addressed to the Underwriters, of Davis Polk & Wardwell LLP, counsel for the Underwriters, with respect to such matters as the Representatives may reasonably request, and such counsel shall have received such documents and information as they may reasonably request to enable them to pass upon such matters.

(j) *Opinion of Counsel for the Depositary.* The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, an opinion of Patterson Belknap Webb & Tyler LLP, counsel for the Depositary, with respect to such matters as the Representatives may reasonably request and in form and substance reasonably satisfactory to the Representatives.

(k) *No Legal Impediment to Issuance and Sale.* No action shall have been taken and no statute, rule, regulation or order shall have been enacted, adopted or issued by any federal, state or foreign governmental or regulatory authority that would, as of the Closing Date or the Additional Closing Date, as the case may be, prevent the issuance or sale of the Offered ADSs; and no injunction or order of any federal, state or foreign court shall have been issued that would, as of the Closing Date or the Additional Closing Date, as the case may be, prevent the issuance or sale of the Offered ADSs.

(l) *Good Standing*. The Representatives shall have received on and as of the Closing Date or the Additional Closing Date, as the case may be, reasonably satisfactory evidence of the good standing of the Company and its subsidiaries in their respective jurisdictions of organization and their good standing in such other jurisdictions as the Representatives may reasonably request, in each case in writing or any standard form of telecommunication from the appropriate governmental authorities of such jurisdictions.

(m) *Exchange Listing.* The ADSs to be delivered on the Closing Date or the Additional Closing Date, as the case may be, shall have been approved for listing on the Nasdaq Market, subject to official notice of issuance.

(n) *Lock-up Agreements*. The "lock-up" agreements, each substantially in the form of Exhibit D hereto, between you and certain shareholders, officers and directors of the Company relating to sales and certain other dispositions of Ordinary Shares, ADSs or certain other securities, delivered to you on or before the date hereof, shall be full force and effect on the Closing Date or the Additional Closing Date, as the case may be.

(o) *Certificates at Closing Date.* The Depositary shall have furnished or caused to be furnished to the Representatives at the Closing Date or Additional Closing Date, as the case may be, certificates reasonably satisfactory to the Representatives evidencing the deposit with it or its nominee of the Shares being so deposited against issuance of the Offered ADSs to be delivered by the Company at the Closing Date or Additional Closing Date, as the case may be, and the execution, countersignature (if applicable), issuance and delivery of such Offered ADSs pursuant to the Deposit Agreement.

(p) *Additional Documents.* On or prior to the Closing Date or the Additional Closing Date, as the case may be, the Company shall have furnished to the Representatives such further certificates and documents as the Representatives may reasonably request.

All opinions, letters, certificates and evidence mentioned above or elsewhere in this Agreement shall be deemed to be in compliance with the provisions hereof only if they are in form and substance reasonably satisfactory to counsel for the Underwriters.

7. Indemnification and Contribution.

(a) *Indemnification of the Underwriters.* The Company agrees to indemnify and hold harmless each Underwriter, its affiliates, directors and officers and each person, if any, who controls such Underwriter within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, from and against any and all losses, claims, damages and liabilities (including, without limitation, documented legal fees and other documented expenses incurred in connection with any suit, action or proceeding or any claim asserted, as such fees and expenses are incurred), joint or several, that arise out of, or are based upon, (i) any untrue statement or alleged untrue statement of a material fact contained in the Registration Statement or caused by any omission or alleged omission to state therein a material fact required to be stated therein or necessary in order to make the statements therein, not misleading, or (ii) any untrue statement or alleged untrue statement of a material fact contained in the Prospectus (or any amendment or supplement thereto), any Preliminary Prospectus, any Issuer Free Writing Prospectus, any "issuer information" filed or required to be filed pursuant to Rule 433(d) under the Securities Act, any Written Testing-the-Waters Communication, any road show as defined in Rule 433(h) under the Securities Act (a "road show") or any Pricing Disclosure Package (including any Pricing Disclosure Package that has subsequently been amended), or caused by any omission or alleged omission to state therein a material fact necessary in order to make the statements therein, in light of the circumstances under which they were made, not misleading, in each case except insofar as such losses, claims, damages or liabilities arise out of, or are based upon, any untrue statement or omission or

alleged untrue statement or omission made in reliance upon and in conformity with any information relating to any Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use therein, it being understood and agreed that the only such information furnished by any Underwriter consists of the information described as such in subsection (b) below.

(b) *Indemnification of the Company.* Each Underwriter agrees, severally and not jointly, to indemnify and hold harmless the Company, its directors, its officers who signed the Registration Statement and each person, if any, who controls the Company within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act to the same extent as the indemnity set forth in paragraph (a) above, but only with respect to any losses, claims, damages or liabilities that arise out of, or are based upon, any untrue statement or omission or alleged untrue statement or omission made in reliance upon and in conformity with any information relating to such Underwriter furnished to the Company in writing by such Underwriter through the Representatives expressly for use in the Registration Statement, the Prospectus (or any amendment or supplement thereto), any Preliminary Prospectus, any Issuer Free Writing Prospectus, any Written Testing-the-Waters Communication, any road show or any Pricing Disclosure Package (including any Pricing Disclosure Package that has subsequently been amended), it being understood and agreed upon that the only such information furnished by any Underwriter consists of the following information in the Prospectus furnished on behalf of each Underwriter: the third paragraph, the first sentence of the twelfth paragraph and the thirteenth, fourteenth and fifteenth paragraphs describing passive market making activities and stabilization under the caption "Underwriting."

(c) *Notice and Procedures.* If any suit, action, proceeding (including any governmental or regulatory investigation), claim or demand shall be brought or asserted against any person in respect of which indemnification may be sought pursuant to the preceding paragraphs of this Section 7, such person (the "Indemnified Person") shall promptly notify the person against whom such indemnification may be sought (the "Indemnifying Person") in writing; provided that the failure to notify the Indemnifying Person shall not relieve it from any liability that it may have under the preceding paragraphs of this Section 7 except to the extent that it has been materially prejudiced (through the forfeiture of substantive rights or defenses) by such failure; and provided, further, that the failure to notify the Indemnifying Person shall not relieve it from any liability that it may have to an Indemnified Person otherwise than under the preceding paragraphs of this Section 9. If any such proceeding shall be brought or asserted against an Indemnified Person and it shall have notified the Indemnifying Person thereof, the Indemnifying Person shall retain counsel reasonably satisfactory to the Indemnified Person (who shall not, without the consent of the Indemnified Person, be counsel to the Indemnifying Person) to represent the Indemnified Person and any others entitled to indemnification pursuant to this Section that the Indemnifying Person may designate in such proceeding and shall pay the documented fees and expenses in such proceeding and shall pay the fees and expenses of such counsel related to such proceeding, as incurred. In any such proceeding, any Indemnified Person shall have the right to retain its own counsel, but the fees and expenses of such counsel shall be at the expense of such Indemnified Person unless (i) the Indemnifying Person and the Indemnified Person shall have mutually agreed to the

contrary; (ii) the Indemnifying Person has failed within a reasonable time to retain counsel reasonably satisfactory to the Indemnified Person; (iii) the Indemnified Person shall have reasonably concluded that there may be legal defenses available to it that are different from or in addition to those available to the Indemnifying Person; or (iv) the named parties in any such proceeding (including any impleaded parties) include both the Indemnifying Person and the Indemnified Person and representation of both parties by the same counsel would be inappropriate due to actual or potential differing interests between them. It is understood and agreed that the Indemnifying Person shall not, in connection with any proceeding or related proceeding in the same jurisdiction, be liable for the fees and expenses of more than one separate firm (in addition to any local counsel) for all Indemnified Persons, and that all such fees and expenses shall be paid or reimbursed as they are incurred. Any such separate firm for any Underwriter, its affiliates, directors and officers and any control persons of such Underwriter shall be designated in writing by the Representatives and any such separate firm for the Company, its directors, its officers who signed the Registration Statement and any control persons of the Company shall be designated in writing by the Company. The Indemnifying Person shall not be liable for any settlement of any proceeding effected without its written consent, but if settled with such consent, the Indemnifying Person agrees to indemnify each Indemnified Person from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time an Indemnified Person shall have requested that an Indemnifying Person reimburse the Indemnified Person for fees and expenses of counsel as contemplated by this paragraph, the Indemnifying Person shall be liable for any settlement of any proceeding effected without its written consent if (i) such settlement is entered into more than 30 days after receipt by the Indemnifying Person of such request and (ii) the Indemnifying Person shall not have reimbursed the Indemnified Person in accordance with such request prior to the date of such settlement. No Indemnifying Person shall, without the written consent of the Indemnified Person, effect any settlement of any pending or threatened proceeding in respect of which any Indemnified Person is or could have been a party and indemnification could have been sought hereunder by such Indemnified Person, unless such settlement (x) includes an unconditional release of such Indemnified Person, in form and substance reasonably satisfactory to such Indemnified Person, from all liability on claims that are the subject matter of such proceeding and (y) does not include any statement as to or any admission of fault, culpability or a failure to act by or on behalf of any Indemnified Person.

(d) *Contribution.* If the indemnification provided for in paragraphs (a) and (b) above is unavailable to an Indemnified Person or insufficient in respect of any losses, claims, damages or liabilities referred to therein, then each Indemnifying Person under such paragraph, in lieu of indemnifying such Indemnified Person thereunder, shall contribute to the amount paid or payable by such Indemnified Person as a result of such losses, claims, damages or liabilities (i) in such proportion as is appropriate to reflect the relative benefits received by the Company, on the one hand, and the Underwriters on the other, from the offering of the Offered ADSs or (ii) if the allocation provided by clause (i) is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause (i) but also the relative fault of the Company, on the one hand, and the Underwriters on the other, in connection with the statements or omissions that resulted in such losses, claims, damages or liabilities, as well

as any other relevant equitable considerations. The relative benefits received by the Company, on the one hand, and the Underwriters on the other, shall be deemed to be in the same respective proportions as the net proceeds (before deducting expenses) received by the Company from the sale of the Offered ADSs and the total underwriting discounts and commissions received by the Underwriters in connection therewith, in each case as set forth in the table on the cover of the Prospectus, bear to the aggregate offering price of the Offered ADSs. The relative fault of the Company, on the one hand, and the Underwriters on the other, shall be determined by reference to, among other things, whether the untrue or alleged untrue statement of a material fact or the omission or alleged omission to state a material fact relates to information supplied by the Company or by the Underwriters and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

(e) *Limitation on Liability.* The Company and the Underwriters agree that it would not be just and equitable if contribution pursuant to paragraph (d) above were determined by pro rata allocation (even if the Underwriters were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in paragraph (d) above. The amount paid or payable by an Indemnified Person as a result of the losses, claims, damages and liabilities referred to in paragraph (d) above shall be deemed to include, subject to the limitations set forth above, any reasonable documented legal or other expenses incurred by such Indemnified Person in connection with any such action or claim. Notwithstanding the provisions of paragraphs (d) and (e), in no event shall an Underwriter be required to contribute any amount in excess of the amount by which the total underwriting discounts and commissions received by such Underwriter with respect to the offering of the ADSs exceeds the amount of any damages that such Underwriter has otherwise been required to pay by reason of such untrue or alleged untrue statement or omission or alleged omission. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The Underwriters' obligations to contribute pursuant to paragraphs (d) and (e) are several in proportion to their respective purchase obligations hereunder and not joint.

(f) *Non-Exclusive Remedies.* The remedies provided for in this Section 7 paragraphs (a) through (e) are not exclusive and shall not limit any rights or remedies which may otherwise be available to any Indemnified Person at law or in equity.

(g) *Directed ADS Program Indemnification.* The Company agrees to indemnify and hold harmless the Directed ADS Underwriter, its affiliates, directors and officers and each person, if any, who controls the Directed ADS Underwriter within the meaning of either Section 15 of the Securities Act or Section 20 of the Exchange Act (each a "Directed ADS Underwriter Entity") from and against any and all losses, claims, damages and liabilities (including, without limitation, any documented legal fees and other expenses incurred in connection with defending or investigating any suit, action or proceeding or any claim asserted, as such fees and expenses are incurred) (i) caused by any untrue statement or alleged untrue statement of a material fact contained in any material prepared by or with the consent of the Company for distribution to Participants

in connection with the Directed ADS Program or caused by any omission or alleged omission to state therein a material fact necessary to make the statements therein, in light of the circumstances under which they were made, not misleading; (ii) caused by the failure of any Participant to pay for and accept delivery of Directed ADSs that the Participant agreed to purchase; or (iii) related to, arising out of, or in connection with the Directed ADS Program, other than losses, claims, damages or liabilities (or expenses relating thereto) that are finally judicially determined to have resulted from the bad faith or gross negligence of the Directed ADS Underwriter Entities.

(h) In case any proceeding (including any governmental investigation) shall be instituted involving any Directed ADS Underwriter Entity in respect of which indemnity may be sought pursuant to paragraph (g) above, the Directed ADS Underwriter Entity seeking indemnity shall promptly notify the Company in writing and the Company, upon request of the Directed ADS Underwriter Entity, shall retain counsel reasonably satisfactory to the Directed ADS Underwriter Entity to represent the Directed ADS Underwriter Entity and any others the Company may designate in such proceeding and shall pay the reasonable fees and disbursements of such counsel related to such proceeding. In any such proceeding, any Directed ADS Underwriter Entity shall have the right to retain its own counsel, but the fees and expenses of such counsel shall be at the expense of such Directed ADS Underwriter Entity unless (i) the Company and such Directed ADS Underwriter Entity shall have mutually agreed to the retention of such counsel, (ii) the Company has failed within a reasonable time to retain counsel reasonably satisfactory to such Directed ADS Underwriter Entity, (iii) the Directed ADS Underwriter Entity shall have reasonably concluded that there may be legal defenses available to it that are different from or in addition to those available to the Company or (iv) the named parties to any such proceeding (including any impleaded parties) include both the Company and the Directed ADS Underwriter Entity and representation of both parties by the same counsel would be inappropriate due to actual or potential differing interests between them. The Company shall not, in respect of the legal expenses of the Directed ADS Underwriter Entities in connection with any proceeding or related proceedings in the same jurisdiction, be liable for the fees and expenses of more than one separate firm (in addition to any local counsel) for all Directed ADS Underwriter Entities. The Company shall not be liable for any settlement of any proceeding effected without its written consent, but if settled with such consent, the Company agrees to indemnify the Directed ADS Underwriter Entities from and against any loss or liability by reason of such settlement. Notwithstanding the foregoing sentence, if at any time any Directed ADS Underwriter Entity shall have requested the Company to reimburse such Directed ADS Underwriter Entity for fees and expenses of counsel as contemplated by the second and third sentences of this paragraph, the Company agrees that it shall be liable for any settlement of any proceeding effected without its written consent if (i) such settlement is entered into more than 30 days after receipt by the Company of the aforesaid request and (ii) the Company shall not have reimbursed such Directed ADS Underwriter Entity in accordance with such request prior to the date of such settlement. The Company shall not, without the prior written consent of the Directed ADS Underwriter, effect any settlement of any pending or threatened proceeding in respect of which any Directed ADS Underwriter Entity is or could have been a party and indemnity could have been sought hereunder by such Directed ADS Underwriter Entity, unless (x) such settlement

includes an unconditional release of the Directed ADS Underwriter Entities from all liability on claims that are the subject matter of such proceeding and (y) does not include any statement as to or any admission of fault, culpability or a failure to act by or on behalf of the Directed ADS Underwriter Entity.

(i) To the extent the indemnification provided for in paragraph (g) above is unavailable to a Directed ADS Underwriter Entity or insufficient in respect of any losses, claims, damages or liabilities referred to therein, then the Company in lieu of indemnifying the Directed ADS Underwriter Entity thereunder, shall contribute to the amount paid or payable by the Directed ADS Underwriter Entity as a result of such losses, claims, damages or liabilities (1) in such proportion as is appropriate to reflect the relative benefits received by the Company on the one hand and the Directed ADS Underwriter Entities on the other hand from the offering of the Directed ADSs or (2) if the allocation provided by clause 7(i)(1) above is not permitted by applicable law, in such proportion as is appropriate to reflect not only the relative benefits referred to in clause 7(i)(1) above but also the relative fault of the Company on the one hand and of the Directed ADS Underwriter Entities on the other hand in connection with any statements or omissions that resulted in such losses, claims, damages or liabilities, as well as any other relevant equitable considerations. The relative benefits received by the Company on the one hand and the Directed ADS Underwriter Entities on the other hand in connection with the offering of the Directed ADSs shall be deemed to be in the same respective proportions as the net proceeds from the offering of the Directed ADSs (before deducting expenses) and the total underwriting discounts and commissions received by the Directed ADS Underwriter Entities for the Directed ADSs, bear to the aggregate public offering price of the Directed ADSs. If the loss, claim, damage or liability is caused by an untrue or alleged untrue statement of material fact or the omission or alleged omission to state a material fact, the relative fault of the Company on the one hand and the Directed ADS Underwriter Entities on the other hand shall be determined by reference to, among other things, whether the untrue or alleged untrue statement or the omission or alleged omission relates to information supplied by the Company or by the Directed ADS Underwriter Entities and the parties' relative intent, knowledge, access to information and opportunity to correct or prevent such statement or omission.

(j) The Company and the Directed ADS Underwriter Entities agree that it would be not just or equitable if contribution pursuant to paragraph (i) above were determined by pro rata allocation (even if the Directed ADS Underwriter Entities were treated as one entity for such purpose) or by any other method of allocation that does not take account of the equitable considerations referred to in paragraph (i) above. The amount paid or payable by the Directed ADS Underwriter Entities as a result of the losses, claims, damages and liabilities referred to in the immediately preceding paragraph shall be deemed to include, subject to the limitations set forth above, any documented legal or other expenses reasonably incurred by the Directed ADS Underwriter Entities in connection with investigating or defending such any action or claim. Notwithstanding the provisions of paragraph (i) above, no Directed ADS Underwriter Entity shall be required to contribute any amount in excess of the amount by which the total price at which the Directed ADSs distributed to the public were offered to the public exceeds the amount of any damages that such Directed ADS Underwriter Entity has otherwise been

required to pay. No person guilty of fraudulent misrepresentation (within the meaning of Section 11(f) of the Securities Act) shall be entitled to contribution from any person who was not guilty of such fraudulent misrepresentation. The remedies provided for in paragraphs (g) through (j) are not exclusive and shall not limit any rights or remedies which may otherwise be available to any indemnified party at law or in equity.

(k) The indemnity and contribution provisions contained in paragraphs (g) through (j) shall remain operative and in full force and effect regardless of (i) any termination of this Agreement, (ii) any investigation made by or on behalf of any Directed ADS Underwriter Entity or the Company, its officers or directors or any person controlling the Company and (iii) acceptance of and payment for any of the Directed ADSs.

8. Effectiveness of Agreement. This Agreement shall become effective as of the date first written above.

9. Termination. This Agreement may be terminated in the absolute discretion of the Representatives, by notice to the Company, if after the execution and delivery of this Agreement and on or prior to the Closing Date or, in the case of the Option ADSs, prior to the Additional Closing Date (i) trading generally shall have been suspended or materially limited on or by either the New York Stock Exchange or The Nasdaq Stock Market; (ii) trading of any securities issued or guaranteed by the Company shall have been suspended on any exchange or in any over-the-counter market; (iii) a general moratorium on commercial banking activities shall have been declared by federal or New York State authorities; or (iv) there shall have occurred any outbreak or escalation of hostilities or any change in financial markets or any calamity or crisis, either within or outside the United States, that, in the judgment of the Representatives, is material and adverse and makes it impracticable or inadvisable to proceed with the offering, sale or delivery of the Offered ADSs on the Closing Date or the Additional Closing Date, as the case may be, on the terms and in the manner contemplated by this Agreement, the Pricing Disclosure Package and the Prospectus.

10. Defaulting Underwriter.

(a) If, on the Closing Date or the Additional Closing Date, as the case may be, any Underwriter defaults on its obligation to purchase the Offered ADSs that it has agreed to purchase hereunder on such date, the non-defaulting Underwriters may in their discretion arrange for the purchase of such Offered ADSs by other persons satisfactory to the Company on the terms contained in this Agreement. If, within 36 hours after any such default by any Underwriter, the non-defaulting Underwriters do not arrange for the purchase of such Offered ADSs, then the Company shall be entitled to a further period of 36 hours within which to procure other persons satisfactory to the non-defaulting Underwriters to purchase such Offered ADSs on such terms. If other persons become obligated or agree to purchase the Offered ADSs of a defaulting Underwriter, either the non-defaulting Underwriters or the Company may postpone the Closing Date or the Additional Closing Date, as the case may be, for up to five full business days in order to effect any changes that in the opinion of counsel for the Company or counsel for the Underwriters may be necessary in the Registration Statement and the Prospectus or in

any other document or arrangement, and the Company agrees to promptly prepare any amendment or supplement to the Registration Statement and the Prospectus that effects any such changes. As used in this Agreement, the term "Underwriter" includes, for all purposes of this Agreement unless the context otherwise requires, any person not listed in Schedule 1 hereto that, pursuant to this Section 10, purchases Offered ADSs that a defaulting Underwriter agreed but failed to purchase.

(b) If, after giving effect to any arrangements for the purchase of the Offered ADSs of a defaulting Underwriter or Underwriters by the non-defaulting Underwriters and the Company as provided in paragraph (a) above, the aggregate number of Offered ADSs that remain unpurchased on the Closing Date or the Additional Closing Date, as the case may be, does not exceed one-eleventh of the aggregate number of Offered ADSs to be purchased on such date, then the Company shall have the right to require each non-defaulting Underwriter to purchase the number of Offered ADSs that such Underwriter agreed to purchase hereunder on such date plus such Underwriter's pro rata share (based on the number of Offered ADSs that such Underwriter agreed to purchase on such date) of the Offered ADSs of such defaulting Underwriter or Underwriters for which such arrangements have not been made.

(c) If, after giving effect to any arrangements for the purchase of the Offered ADSs of a defaulting Underwriter or Underwriters by the non-defaulting Underwriters and the Company as provided in paragraph (a) above, the aggregate number of Offered ADSs that remain unpurchased on the Closing Date or the Additional Closing Date, as the case may be, exceeds one-eleventh of the aggregate amount of Offered ADSs to be purchased on such date, or if the Company shall not exercise the right described in paragraph (b) above, then this Agreement or, with respect to any Additional Closing Date, the obligation of the Underwriters to purchase Offered ADSs on the Additional Closing Date, as the case may be, shall terminate without liability on the part of the non-defaulting Underwriters. Any termination of this Agreement pursuant to this Section 10 shall be without liability on the part of the Company, except that the Company will continue to be liable for the payment of expenses as set forth in Section 11 hereof and except that the provisions of Section 7 hereof shall not terminate and shall remain in effect.

(d) Nothing contained herein shall relieve a defaulting Underwriter of any liability it may have to the Company or any non-defaulting Underwriter for damages caused by its default.

11. Payment of Expenses.

(a) Whether or not the transactions contemplated by this Agreement are consummated or this Agreement is terminated, the Company will pay or cause to be paid all costs and expenses incident to the performance of its obligations hereunder, including without limitation, (i) the costs incident to the authorization, issuance, sale, preparation and delivery of the Shares and the Offered ADSs and any taxes payable in that connection; (ii) the costs incident to the preparation, printing and filing under the Securities Act of the Registration Statement, the Preliminary Prospectus, any Issuer Free Writing Prospectus,

any Pricing Disclosure Package and the Prospectus (including all exhibits, amendments and supplements thereto) and the distribution thereof; (iii) the costs of reproducing and distributing each of the Transaction documents; (iv) the fees and expenses of the Company's counsel and independent accountants; (v) the fees and expenses incurred in connection with the registration or qualification and determination of eligibility for investment of the Offered ADSs under the state or foreign securities or blue sky laws of such jurisdictions as the Representatives may designate and the preparation, printing and distribution of a Blue Sky Memorandum (including the related fees and expenses of counsel for the Underwriters); (vi) the cost of preparing stock certificates; (vii) the costs and charges of any transfer agent and any registrar; (viii) all expenses and application fees incurred in connection with any filing with, and clearance of the offering by, FINRA; provided that the aggregate amount payable by the Company pursuant to clauses (v) and (viii) shall not exceed $45,000; (ix) all expenses incurred by the Company in connection with any "road show" presentation to potential investors; provided, however, that the Underwriters shall pay all of the travel, lodging and other expenses of the Underwriters or any of their employees incurred by them in connection with the "road show", and provided further, that the Company and the Underwriters shall each pay 50% of the cost of any aircraft chartered in connection with such "road show"; (x) all expenses and application fees related to the listing of the Offered ADSs on the Nasdaq Market (xi) all of the fees and disbursements of counsel incurred by the Underwriters in connection with the Directed ADS Program and stamp duties, stamp duty reserve tax, similar taxes or duties or other taxes, if any, including any interest and penalties thereon, incurred by the Underwriters in connection with the Directed ADS Program.

(b) If (i) this Agreement is terminated pursuant to Section 9, (ii) the Company for any reason fails to tender the Offered ADSs for delivery to the Underwriters (other than by reason of a default by any Underwriter) or (iii) the Underwriters decline to purchase the Offered ADSs for any reason permitted under this Agreement, the Company agrees to reimburse the Underwriters for all out-of-pocket costs and expenses (including the fees and expenses of their counsel) reasonably incurred by the Underwriters in connection with this Agreement and the offering contemplated hereby.

12. Persons Entitled to Benefit of Agreement. This Agreement shall inure to the benefit of and be binding upon the parties hereto and their respective successors and the officers and directors and any controlling persons referred to herein, and the affiliates of each Underwriter referred to in Section 7 hereof. Nothing in this Agreement is intended or shall be construed to give any other person any legal or equitable right, remedy or claim under or in respect of this Agreement or any provision contained herein. No purchaser of Offered ADSs from any Underwriter shall be deemed to be a successor merely by reason of such purchase.

13. Survival. The respective indemnities, rights of contribution, representations, warranties and agreements of the Company and the Underwriters contained in this Agreement or made by or on behalf of the Company or the Underwriters pursuant to this Agreement or any certificate delivered pursuant hereto shall survive the delivery of and payment for the Offered ADSs and shall remain in full force and effect, regardless of any termination of this Agreement or any investigation made by or on behalf of the Company or the Underwriters or the directors, officers, controlling persons or affiliates referred to in Section 7 hereof.

14. Certain Defined Terms. For purposes of this Agreement, (a) except where otherwise expressly provided, the term "affiliate" has the meaning set forth in Rule 405 under the Securities Act; (b) the term "business day" means any day other than a day on which banks are permitted or required to be closed in New York City; and (c) the term "subsidiary" has the meaning set forth in Rule 405 under the Securities Act.

15. Compliance with USA Patriot Act. In accordance with the requirements of the USA Patriot Act (Title III of Pub. L. 107-56 (signed into law October 26, 2001)), the Underwriters are required to obtain, verify and record information that identifies their respective clients, including the Company, which information may include the name and address of their respective clients, as well as other information that will allow the Underwriters to properly identify their respective clients.

16. Miscellaneous.

(a) *Notices.* All notices and other communications hereunder shall be in writing and shall be deemed to have been duly given if mailed or transmitted and confirmed by any standard form of telecommunication. Notices to the Underwriters shall be given to the Representatives c/o J.P. Morgan Securities LLC, 383 Madison Avenue, New York, New York 10179 (fax: (212) 622-8358), Attention: Equity Syndicate Desk, c/o Goldman Sachs & Co. LLC, 200 West Street, New York, New York 10282, Attention: Control Room and c/o Cowen and Company, LLC, 599 Lexington Avenue, 27th Floor, New York, NY 10022 (fax: (646) 562-1124), Attention: General Counsel. Notices to the Company shall be given to it at Orchard Therapeutics plc, 108 Cannon Street, London EC4N 6EU, United Kingdom; Attention: John Ilett, General Counsel & Company Secretary.

(b) *Governing Law.* This Agreement and any claim, controversy or dispute arising under or related to this Agreement shall be governed by and construed in accordance with the laws of the State of New York.

(c) *Submission to Jurisdiction*. The Company hereby submits to the exclusive jurisdiction of the U.S. federal and New York state courts in the Borough of Manhattan in The City of New York in any suit or proceeding arising out of or relating to this Agreement or the transactions contemplated hereby. The Company waives any objection which it may now or hereafter have to the laying of venue of any such suit or proceeding in such courts. The Company agrees that final judgment in any such suit, action or proceeding brought in such court shall be conclusive and binding upon the Company and may be enforced in any court to the jurisdiction of which Company is subject by a suit upon such judgment. The Company irrevocably appoints Cogency Global Inc., located 10 E. 40th Street, 10th Floor, New York, New York 10016, as its authorized agent in the Borough of Manhattan in The City of New York upon which process may be served in any such suit or proceeding, and agrees that service of process upon such authorized agent, and written notice of such service to the Company by the person serving the same to the address provided in this Section 16, shall be deemed in every respect effective service of process upon the Company in any such suit or proceeding. The Company hereby represents and warrants that such authorized agent has accepted such appointment and

has agreed to act as such authorized agent for service of process. The Company further agrees to take any and all action as may be necessary to maintain such designation and appointment of such authorized agent in full force and effect for a period of seven years from the date of this Agreement.

(d) *MIFID Product Governance*. Solely for the purposes of the requirements of Article 9(8) of the MIFID Product Governance rules under EU Delegated Directive 2017/593 (the "Product Governance Rules") regarding the mutual responsibilities of manufacturers under the Product Governance Rules (i) each manufacturer acknowledges to each other manufacturer that it understands the responsibilities conferred upon it under the Product Governance Rules relating to each of the product approval process, the target market and the proposed distribution channels as applying to the ADSs and the related information set out in the Prospectus in connection with the ADSs; and (ii) the Underwriters and the Company note the application of the Product Governance Rules and acknowledge the target market and distribution channels identified as applying to the ADSs by the manufacturers and the related information set out in the Prospectus in connection with the ADSs.

(e) *Judgment Currency*. The Company agrees to indemnify each Underwriter, its directors, officers, affiliates and each person, if any, who controls such Underwriter within the meaning of Section 15 of the Securities Act or Section 20 of the Exchange Act, against any loss incurred by such Underwriter as a result of any judgment or order being given or made for any amount due hereunder and such judgment or order being expressed and paid in a currency (the "judgment currency") other than U.S. dollars and as a result of any variation as between (i) the rate of exchange at which the U.S. dollar amount is converted into the judgment currency for the purpose of such judgment or order, and (ii) the rate of exchange at which such indemnified person is able to purchase U.S. dollars with the amount of the judgment currency actually received by the indemnified person. The foregoing indemnity shall constitute a separate and independent obligation of the Company and shall continue in full force and effect notwithstanding any such judgment or order as aforesaid. The term "rate of exchange" shall include any premiums and costs of exchange payable in connection with the purchase of, or conversion into, the relevant currency.

(f) *Waiver of Immunity*. To the extent that the Company has or hereafter may acquire any immunity (sovereign or otherwise) from jurisdiction of any court of (i) England and Wales, (ii) the United States or the State of New York, (iii) any jurisdiction in which it owns or leases property or assets or from any legal process (whether through service of notice, attachment prior to judgment, attachment in aid of execution, execution, set-off or otherwise) with respect to themselves or their respective property and assets or this Agreement, the Company hereby irrevocably waives such immunity in respect of its obligations under this Agreement to the fullest extent permitted by applicable law.

(g) *Waiver of Jury Trial.* Each of the parties hereto hereby waives any right to trial by jury in any suit or proceeding arising out of or relating to this Agreement.

(h) *Counterparts.* This Agreement may be signed in counterparts (which may include counterparts delivered by any standard form of telecommunication), each of which shall be an original and all of which together shall constitute one and the same instrument.

(i) *Amendments or Waivers.* No amendment or waiver of any provision of this Agreement, nor any consent or approval to any departure therefrom, shall in any event be effective unless the same shall be in writing and signed by the parties hereto.

(j) *Headings.* The headings herein are included for convenience of reference only and are not intended to be part of, or to affect the meaning or interpretation of, this Agreement.

If the foregoing is in accordance with your understanding, please indicate your acceptance of this Agreement by signing in the space provided below.

Very truly yours,

ORCHARD THERAPEUTICS plc

By: _____
Name:
Title:

Accepted: As of the date first written above

J.P. MORGAN SECURITIES LLC
GOLDMAN SACHS & CO. LLC
COWEN AND COMPANY, LLC

For itself and on behalf of the
several Underwriters listed
in Schedule 1 hereto.

J.P. MORGAN SECURITIES LLC

By: _____
Authorized Signatory

GOLDMAN SACHS & CO. LLC

By: _____
Authorized Signatory

COWEN AND COMPANY, LLC

By: _____
Authorized Signatory

Underwriter	Number of Underwritten ADSs
J.P. Morgan Securities LLC	
Goldman Sachs & Co. LLC	
Cowen and Company, LLC	
Wedbush Securities Inc.	
Total	

a. **Pricing Disclosure Package**

[●]

[b. **Pricing Information Provided Orally by Underwriters]**

[●]

Written Testing-the-Waters Communications

[None]

Orchard Therapeutics plc

Pricing Term Sheet

EGC – Testing the waters authorization (to be delivered by the issuer to the Representatives in email or letter form)

In reliance on Section 5(d) of the Securities Act of 1933, as amended (the "Act"), Orchard Rx Limited (the "Issuer") hereby authorizes J.P. Morgan Securities LLC ("J.P. Morgan"), Goldman Sachs & Co. LLC ("Goldman") and Cowen and Company, LLC ("Cowen") and their respective affiliates and employees, to engage on behalf of the Issuer in oral and written communications with potential investors that are "qualified institutional buyers", as defined in Rule 144A under the Act, or institutions that are "accredited investors", as defined in Regulation D under the Act, to determine whether such investors might have an interest in the Issuer's contemplated initial public offering ("Testing-the-Waters Communications"). A "Written Testing-the Waters Communication" means any Testing-the-Waters Communication that is a written communication within the meaning of Rule 405 under the Act.

It is our and your expectation that, unless otherwise approved by the Issuer or J.P. Morgan, Goldman and Cowen, the Issuer, J.P. Morgan, Goldman and Cowen and their respective affiliates and employees will not send or give to any potential investor any Written Testing-the-Waters-Communication other than such Testing-the-Waters-Communications that are limited to any one or more statements described in Rule 134 under the Act (whether or not reliance on Rule 134 would otherwise be permitted or available under the Act for such Testing-the-Waters-Communication) and/or any customary legal or regulatory legends or disclaimers.

The Issuer represents that it is an "emerging growth company" as defined in Section 2(a)(19) of the Act ("Emerging Growth Company") and agrees to promptly notify J.P. Morgan, Goldman and Cowen in writing if the Issuer hereafter ceases to be an Emerging Growth Company while this authorization is in effect. If at any time following the distribution of any Written Testing-the-Waters Communication there occurs an event or development as a result of which such Written Testing-the-Waters Communication included or would include an untrue statement of a material fact or omitted or would omit to state a material fact necessary in order to make the statements therein, in the light of the circumstances existing at that subsequent time, not misleading, the Issuer will promptly notify J.P. Morgan, Goldman and Cowen and will promptly amend or supplement, at its own expense, such Written Testing-the-Waters Communication to eliminate or correct such untrue statement or omission.

Nothing in this authorization is intended to limit or otherwise affect the ability of J.P. Morgan, Goldman and Cowen and their respective affiliates and employees, to engage in communications in which they could otherwise lawfully engage in the absence of this authorization, including, without limitation, any written communication containing only one or more of the statements specified under Rule 134(a) under the Act. This authorization shall remain in effect until the Issuer has provided to J.P. Morgan, Goldman and Cowen a written notice revoking this authorization. All notices as described herein shall be sent by email to the attention of David Ke at david.ke@jpmorgan.com, Jack Bannister at jack.bannister@gs.com and Mariel Healy at mariel.healy@cowen.com, with copies to Deanna Kirkpatrick at Deanna.kirkpatrick@davispolk.com and Andrew Terjesen at andrew.terjesen@davispolk.com.

Exhibit B

J.P. MORGAN SECURITIES LLC
GOLDMAN SACHS & CO. LLC
COWEN AND COMPANY, LLC

Corporation
Public Offering of Common Stock

, 20

[Name and Address of
Officer or Director
Requesting Waiver]

Dear Mr./Ms. [Name]:

This letter is being delivered to you in connection with the offering by Orchard Therapeutics plc (the "Company") of American Depositary Shares, representing ordinary shares, nominal value £0.10 per share (the "Ordinary Shares") of the Company (the "Underwritten ADSs") and the lock-up letter dated , 20 (the "Lock-up Letter"), executed by you in connection with such offering, and your request for a [waiver] [release] dated , 20 _, with respect to Underwritten ADSs (the "ADSs").

J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC hereby agree to [waive] [release] the transfer restrictions set forth in the Lock-up Letter, but only with respect to the ADSs, effective , 20 ; provided, however, that such [waiver] [release] is conditioned on the Company announcing the impending [waiver] [release] by press release through a major news service at least two business days before effectiveness of such [waiver] [release]. This letter will serve as notice to the Company of the impending [waiver] [release].

Except as expressly [waived] [released] hereby, the Lock-up Letter shall remain in full force and effect.

Yours very truly,

[Signature of J.P. Morgan Securities LLC Representative]

[Name of J.P. Morgan Securities LLC Representative]

[Signature of Goldman Sachs & Co. LLC Representative]

[Name of Goldman Sachs & Co. LLC Representative]

[Signature of Cowen and Company, LLC Representative]

[Name of Cowen and Company, LLC Representative]

cc: Orchard Therapeutics plc

[Form of Press Release]

Orchard Therapeutics plc
[Date]

Orchard Therapeutics plc ("Company") announced today that J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC, joint book-running managers in the Company's recent public sale of American Depositary Shares ("ADSs"), representing ordinary shares, nominal value £0.10 per share, are [waiving] [releasing] a lock-up restriction with respect to ADSs of the Company held by [certain officers or directors] [an officer or director] of the Company. The [waiver] [release] will take effect on , 20 , and the ADSs may be sold on or after such date.

This press release is not an offer for sale of the securities in the United States or in any other jurisdiction where such offer is prohibited, and such securities may not be offered or sold in the United States absent registration or an exemption from registration under the United States Securities Act of 1933, as amended.

Exhibit D

FORM OF LOCK-UP AGREEMENT

, 2018

J.P. MORGAN SECURITIES LLC
GOLDMAN SACHS & CO. LLC
COWEN AND COMPANY, LLC

As Representatives of the several Underwriters listed
in Schedule 1 to the Underwriting Agreement defined below

c/o J.P. Morgan Securities LLC
383 Madison Avenue
New York, New York 10179

c/o Goldman Sachs & Co. LLC
200 West Street
New York, New York 10282-2198

c/o Cowen and Company, LLC
599 Lexington Avenue
New York, New York 10022

Re: Orchard Therapeutics plc – Public Offering

Ladies and Gentlemen:

The undersigned is a director, officer or record or beneficial owner of ordinary shares, nominal value £0.00001 per share, of Orchard Therapeutics Limited ("Orchard"), or of securities convertible into or exchangeable or exercisable for ordinary shares of Orchard. Subsequent to the date hereof, Orchard proposes to effect a reorganization pursuant to which the undersigned will exchange its ordinary shares of Orchard, and all securities convertible into or exchangeable or exercisable for ordinary shares of Orchard, for equivalent equity interests in Orchard Therapeutics plc, a newly incorporated English holding company (the "Company," and such transaction, the "Share Exchange"). The undersigned understands that you, as Representatives (the "Representatives") of the several Underwriters named in Schedule 1 to the Underwriting Agreement (the "Underwriters"), propose to enter into an underwriting agreement (the "Underwriting Agreement") with the Company, providing for the public offering (the "Public Offering") by the several Underwriters, of American Depository Shares ("ADSs") of the Company representing ordinary shares nominal value £0.10 per share (the "Securities"). Capitalized terms used herein and not otherwise defined shall have the meanings set forth in the Underwriting Agreement.

In consideration of the Underwriters' agreement to purchase and make the Public Offering of the Securities, and for other good and valuable consideration receipt of which is hereby acknowledged, the undersigned hereby agrees that, without the prior written consent of the Representatives on behalf of the Underwriters, the undersigned will not, during the period beginning on the date of this letter agreement

(this "Letter Agreement") and ending 180 days after the date of the final prospectus relating to the Public Offering (the "Prospectus") (such period, the "Restricted Period"), (1) offer, pledge, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase, or otherwise transfer or dispose of, directly or indirectly, any Ordinary Shares or Related Securities, or publicly disclose the intention to make any offer, sale, pledge or disposition, (2) enter into any swap or other agreement that transfers, in whole or in part, any of the economic consequences of ownership of the Ordinary Shares or such other securities, whether any such transaction described in clause (1) or (2) above is to be settled by delivery of Ordinary Shares or such other securities, in cash or otherwise or (3) make any demand for or exercise any right with respect to the registration of any Ordinary Shares or any security convertible into or exercisable or exchangeable for Ordinary Shares, in each case other than:

(A) the Securities to be sold by the undersigned pursuant to the Underwriting Agreement;

(B) participation in the Share Exchange, provided that any ADSs or Ordinary Shares received by the undersigned pursuant to this clause (B) shall be subject to the terms of this Agreement;

(C) the deposit of Ordinary Shares with the depositary, in exchange for the issuance of ADSs, or the cancellation of ADSs in exchange for the issuance of Ordinary Shares; provided that such ADSs or Ordinary Shares issued pursuant to this clause (C) held by the undersigned shall remain subject to the terms of this Agreement;

(D) sales or transfers of ADSs or Ordinary Shares acquired in the Public Offering or in open market transactions on or after the consummation of the Public Offering;

(E) transfers of Ordinary Shares or Related Securities (i) as a bona fide gift or gifts, (ii) by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the undersigned in a transaction not involving a disposition for value or (iii) pursuant to a court order in respect of, or by operation of law as a result of, a divorce, in a transaction not involving disposition for value;

(F) if the undersigned is (i) an individual, transfers of Ordinary Shares or Related Securities in a transaction not involving a disposition for value to any trust for the direct or indirect benefit of the undersigned or the immediate family of the undersigned, or limited partnerships the partners of which are the undersigned and/or the immediate family members of the undersigned, in each case for estate planning purposes, (ii) a corporation, limited liability company, partnership (whether general, limited or otherwise) or other entity, distributions of Ordinary Shares or Related Securities to current or former members, stockholders, limited partners, general partners, subsidiaries or affiliates (as defined in Rule 405 promulgated under the Securities Act of 1933, as amended) of the undersigned, or to any investment fund or other entity that controls or manages the undersigned (including, for the avoidance of doubt, a fund managed by the same manager or managing member or general partner or management company or by an entity controlling, controlled by, or under common control with such manager or managing member or general partner or management company as the undersigned or who shares a common investment advisor with the undersigned) not involving a disposition for value, or (iii) a trust, distributions of Ordinary Shares or Related Securities to its beneficiaries in a transaction not involving a disposition for value;

(G) the receipt by the undersigned of Ordinary Shares in connection with the conversion of the outstanding preferred shares of the Company upon the consummation of the Public Offering into Ordinary Shares; provided that any such Ordinary Shares received by the undersigned shall be subject to the terms of this Letter Agreement;

(H) the exercise of an option or other equity award to purchase Ordinary Shares or ADSs, as applicable, which are set to expired during the Restricted Period and have been granted under any of the Company's or Orchard's current or future equity incentive plans or equity purchase plans described in the Prospectus and any transfers or dispositions of ADSs, Ordinary Shares or other securities to the Company in connection with the exercise of any such option or equity award; provided that any such ADSs or Ordinary Shares received by the undersigned shall be subject to the terms of this Letter Agreement;

(I) any transfer or disposition in connection with a change of control (it being further understood that this Letter Agreement shall not restrict the undersigned from entering into any agreement or arrangement in connection therewith, including an agreement to vote in favor of, or tender ADSs, Ordinary Shares or other securities of the Company in, any such transaction or taking or not taking any other action in connection with any such transaction); provided that in the event that the acquisition, merger, consolidation or other transaction in connection with such change of control is not completed, the ADSs or Ordinary Shares owned by the undersigned shall remain subject to the restrictions contained in this Letter Agreement; and

(J) the entering into by the undersigned of a written trading plan ("Rule 10b5-1 Plan") pursuant to Rule 10b5-1 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") during the Restricted Period, provided that no sales or transfers of shares of the undersigned's ADSs or Ordinary Shares shall be made pursuant to such Rule 10b5-1 Plan prior to the expiration of the Restricted Period and no filing under the Exchange Act or other public announcement shall be required or voluntarily made by the undersigned or any other person in connection therewith without the permission of the Representatives, prior to the expiration of the Restricted Period;

provided that in the case of any transfer or distribution pursuant to clauses (E), (F) or (I), each donee or distributee shall execute and deliver to the Representative a lock-up letter in the form of this paragraph; and provided, further, that in the case of any transfer or distribution pursuant to clauses (D), (E), (F), (G) or (I), no filing by any party (donor, donee, transferor or transferee) under the Securities Exchange Act of 1934, as amended, or other public announcement shall be required or shall be made voluntarily in connection with such transfer or distribution. If the undersigned is an officer or director of the Company, the undersigned further agrees that the foregoing provisions shall be equally applicable to any Company-directed Securities the undersigned may purchase in the Public Offering.

For purposes of this Letter Agreement, (i) "immediate family" shall mean any relationship by blood, marriage or adoption, not more remote than first cousin, (ii) "Related Securities" shall mean any ADSs, options or warrants or other rights to acquire ADSs or Ordinary Shares or any securities exchangeable or exercisable for or convertible into ADSs or Ordinary Shares, or to acquire other securities or rights ultimately exchangeable or exercisable for or convertible into ADSs or Ordinary Shares, including ordinary shares of Orchard, or securities convertible into or exchangeable or exercisable for ordinary shares of Orchard, held prior to the date of the Share Exchange, and (iii) "change of control" shall mean any bona fide third-party tender offer, merger, consolidation or other similar transaction that is approved by the Board of Directors of the Company and made to all holders of the Company's Ordinary Shares or ADSs, as applicable, in each case, the result of which is that any "person" (as defined in Section 13(d)(3) of the Exchange Act), or group of persons, other than the Company, becomes the beneficial owner (as defined in Rules 13d-3 and 13d-5 of the Exchange Act) of a majority of total voting power of the voting stock of the Company.

If the undersigned is an officer or director of the Company, (i) the Representatives on behalf of the Underwriters agree that, at least three business days before the effective date of any release or waiver of the foregoing restrictions in connection with a transfer of Ordinary Shares or Related Securities, the Representatives on behalf of the Underwriters will notify the Company of the impending release or waiver, and (ii) the Company has agreed in the Underwriting Agreement to announce the impending release or

waiver by press release through a major news service at least two business days before the effective date of the release or waiver. Any release or waiver granted by the Representatives on behalf of the Underwriters hereunder to any such officer or director shall only be effective two business days after the publication date of such press release. The provisions of this paragraph will not apply if (a) the release or waiver is effected solely to permit a transfer not for consideration and (b) the transferee has agreed in writing to be bound by the same terms described in this Letter Agreement to the extent and for the duration that such terms remain in effect at the time of the transfer.

The undersigned hereby waives any and all notice and consent requirements and any other rights of the undersigned with regard to the Company's intention to file the Registration Statement and to the Public Offering of the Securities.

In furtherance of the foregoing, the Company, and any duly appointed transfer agent for the registration or transfer of the securities described herein, are hereby authorized to decline to make any transfer of securities if such transfer would constitute a violation or breach of this Letter Agreement.

The undersigned hereby represents and warrants that the undersigned has full power and authority to enter into this Letter Agreement. All authority herein conferred or agreed to be conferred and any obligations of the undersigned shall be binding upon the successors, assigns, heirs or personal representatives of the undersigned.

The undersigned understands that, if the Underwriting Agreement does not become effective by June 30, 2019, or if the Underwriting Agreement (other than the provisions thereof which survive termination) shall terminate or be terminated prior to payment for and delivery of the Securities to be sold thereunder, the undersigned shall be released from all obligations under this Letter Agreement. The undersigned understands that the Underwriters are entering into the Underwriting Agreement and proceeding with the Public Offering in reliance upon this Letter Agreement.

This Letter Agreement and any claim, controversy or dispute arising under or related to this Letter Agreement shall be governed by and construed in accordance with the laws of the State of New York.

Very truly yours,

[*NAME OF STOCKHOLDER*]

By: _____
Name:
Title:

Exhibit 2.1

EXECUTION VERSION

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "[***]". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT PURSUANT TO RULE 406 PROMULGATED UNDER THE SECURITIES ACT OF 1933, AS AMENDED.

GLAXO GROUP LIMITED

and

GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD.

and

ORCHARD THERAPEUTICS LIMITED

ASSET PURCHASE AND LICENCE AGREEMENT

KING & SPALDING

*** Confidential Treatment Requested ***

CONTENTS

DATE: 11th April 2018

PARTIES:

(1) **ORCHARD THERAPEUTICS LIMITED**, a company incorporated under the laws of England and Wales with registered number 09759506 and having its registered office at Birchin Court, 20 Birchin Lane, London, EC3V 9DU, England, (the "**Purchaser**");

(2) **GLAXO GROUP LIMITED**, a company incorporated under the laws of England, with registered number 00305979 and whose registered office is located at 980 Great West Road, Brentford, Middlesex, TW8 9GS, England ("**Glaxo Group**"); and

(3) **GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LTD**, a company incorporated under the laws of England and Wales with registered number 08283222 and whose registered office is at 980 Great West Road, Brentford, Middlesex, TW8 9GS, England **("GSK IPD")**.

each a "**party**" and, together, the "**parties**". Save as where otherwise provided, Glaxo Group and GSK IPD shall be jointly referred to as the "**Seller**".

RECITALS:

(A) The Seller and/or its Affiliates have been carrying on, inter alia, activities in the rare disease gene therapy space.

(B) In furtherance of these activities, and pursuant to the Telethon-HSR Agreement (as defined below), the Seller has collaborated with Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**HSR**") (Telethon and HSR acting through their jointly established San Raffaele-Telethon Institution for Gene Therapy, an entity without juridical personality) (Telethon and HSR may herein after be referred to collectively as "**Telethon-HSR**") to research and develop stem cell gene therapy programmes with respect to the Programmes (as defined below).

(C) Under the Telethon-HSR Agreement, the Seller has obtained certain exclusive licenses to the ADA-SCID Programme, the WAS Programme, the MLD Programme, and Beta-Thal/Sickle Cell Programme (in each case, as defined below), and has an exclusive option to exclusively license the remaining Programmes. The Seller owns certain assets and owns or has the right to utilise certain intellectual property rights which support its research, development and commercialisation efforts on the Programmes.

(D) The Programmes have to date resulted in one product which has been brought to market by the Seller, namely Strimvelis.

(E) The Seller has determined to divest of its rare diseases assets to which the Programmes relate and accordingly the Seller has agreed to sell or procure to be sold and the Purchaser has agreed to purchase the Assets, and the Seller has further agreed to grant certain licenses related to the Assets to the Purchaser, in each case on the terms set out in this Agreement.

IT IS AGREED as follows:

1. INTERPRETATION

1.1 Defined terms

In this Agreement, the following words and expressions shall have the following meanings:

"**Acquired Domain Names**" means all right, title and interest of the Seller or its Affiliates in the domain names listed in part 1 of Schedule 8;

"**Acquired Trademarks**" means all right, title and interest of Seller or its Affiliates in the trademark applications and registrations listed in part 2 of Schedule 8;

"**ADA-SCID**" means adenosine deaminase severe combined immunodeficiency;

"**ADA-SCID Programme**" means the research, development and commercialisation programme with respect to ADA-SCID that was conducted prior to Completion by Telethon-HSR or Seller and its Affiliates and following Completion, such programme that continues to be conducted by Purchaser and its Affiliates and/or their licensees and assignees utilising, inter alia, the Assets, the Patient-Level Clinical Data or the Licensed Know-How;

"**Additional Consideration**" means any royalties or milestone payments payable with respect to the Royalty Products in accordance with clause 5.3;

"**Adverse Event**" shall have the meaning given to it in the finalised ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines relating to post-approval safety data management definitions and standards for expedited reporting;

"**Adverse Event and Safety Data**" means: (i) the periodic safety update reports (PSURs) for Strimvelis as at Completion or that are generated from time to time up to and including the TSA Expiration Date and provided to the Purchaser pursuant to the terms of the Safety Data Exchange Agreement, together with details of any reported Adverse Events pertaining to Strimvelis since the date of the PSURs; and (ii) details of any urgent safety restrictions imposed by a Regulatory Authority or other Governmental Entity pertaining to the Programmes and Strimvelis as at Completion or that is generated from time to time up to and including the termination or expiry of the Safety Data Exchange Agreement; and (iii) any other material safety and pharmacovigilance data pertaining to the Programmes and/or Strimvelis as at Completion or that is generated from time to time up to and including the termination or expiry of the Safety Data Exchange Agreement;

"**Affiliate**" means, with respect to a person, any other person that Controls or is under Control of such person or is, together with such person, under common Control of a third person;

"Arising Programme IP" means the Intellectual Property generated and Controlled by the Purchaser and its Affiliates in the conduct of activities under the Programmes;

"**Assets**" means those assets which are to be sold and transferred to the Purchaser under this Agreement as defined in clause 2.1;

"**Assignment Transaction**" has the meaning defined in clause 5.5(d);

"**Assumed Liabilities**" has the meaning defined in clause 7.1;

"**Audit Disagreement**" has the meaning defined in clause 13.2(a);

"**Audited Entities**" has the meaning defined in clause 13.1(a);

"**Best Endeavours**" such endeavours as are consistent with the efforts a prudent and determined person intent of achieving a result would expend in similar circumstances to achieve such result;

"**Beta-Thal/Sickle Cell Programme**" means the gene therapy research, development and commercialisation programme with respect to Beta-Thalassemia (excluding the GSK Stable Cell Line) that was conducted prior to Completion by Telethon-HSR or Seller and its Affiliates and following Completion, such programme that continues to be conducted by Purchaser and its Affiliates utilising, inter alia, the Assets, the Patient-Level Clinical Data or the Licensed Know-How;

"**BioSimilar Competitive Product**" means a Gene Therapy Product which has been granted a Product Registration and which relies in some manner on or references or is the Royalty Product MA for approval and demonstrates significant similarity to the relevant Royalty Product in terms of quality, characteristics, biological and/or pharmacological activity, and safety and efficacy. For the avoidance of doubt OTL-101, Strimvelis and/or any other product of the Purchaser or its Affiliates and/or Royalty Product will not be considered BioSimilar Competitive Products of one another;

"**BioSimilar Region**" means each of (i) EU, (ii) US, (iii) Japan and (iv) rest of world;

"**Business Contracts**" means all (i) agreements listed in Schedule 9 and (ii) Novated Contracts;

"**Business Day**" means a day (excluding Saturday or Sunday or a public holiday in England) on which banks generally are open in the City of London, England for the transaction of normal banking business and excluding the period from 24 December to 2 January in which the corporate offices of the Seller are closed for business;

"**Business Intellectual Property**" means the following Intellectual Property owned by the Seller and its Affiliates at the Completion Date:

(a) the Acquired Trademarks; and

(b) the Acquired Domain Names,

but for the avoidance of doubt shall exclude the Licensed Know-How;

"**Calendar Quarter**" means the respective periods of three (3) consecutive calendar months ending on March 31, June 30, September 30 and December 31 respectively;

"**Calendar Year**" means the period of twelve (12) months commencing 1 January;

"**Cassette-Insert**" means the transgene expression cassette containing the specific therapeutic transgene for a Programme, excluding the Unoptioned Programmes. For the avoidance of doubt, the Cassette-Insert specifically excludes virus-derived sequences present in the transfer vector and any sequences used to express virus-derived packaging components in viral vector producer cells such as gagpol, rev and envelope;

"**Change of Control**" shall be deemed to have occurred when (i) any person or persons other than those who Control the Purchaser at the Completion Date subsequently acquire Control of it by means of any transaction or series of related transactions; or (ii) an IPO of the Purchaser occurs.

"**Claim**" means any claim whatsoever made by one party or any other member of the relevant party's group of companies against the other party for breach of, or in connection with, this Agreement (including in the case of a claim by the Purchaser or a member of the Purchaser's group of companies for breach of the Seller's Warranties), whether in contract or tort (including negligence) or in respect of any claim under any indemnity, covenant or undertaking given by the other party under this Agreement;

"**Claimant**" means a party and any of its Affiliates which may be entitled to make a Claim or that brings a Claim;

"**Clinical Data**" means (other than where constituting Patient-Level Clinical Data), to the extent in existence at the Completion Date or generated from time to time up to and including the TSA Expiration Date and in the control of the Seller:

(a) the Clinical Trial Master File Information; and

(b) the Adverse Event and Safety Data,

in each case, in the form in which it is held by or on behalf of the Seller;

"**Clinical Trial Master File Information**" means, to the extent in existence at the Completion Date or that is generated from time to time up to and including the TSA Expiration Date and in the control of the Seller, the collection of study level documents in electronic format together with the related metadata described in Exhibit 1 as maintained in the applicable data location;

"**CMC Know-How**" means developments and inventions made by or on behalf of the Seller or its Affiliates relating to (i) [***]; (ii) [***]; and (iii) [***];

"**Combination Product**" means a product that contains a Royalty Product component and at least one other active component where both or all products are sold and invoiced as one product (with an aggregate price);

"**Commercial Information**" means, the information which is owned by and in the possession of, the Seller or any of its Affiliates and which is listed in Exhibit 2 (in the form in which it is held by the Seller);

"**Commercially Reasonable Efforts**" means such efforts that are consistent with the efforts and resources normally used by the Purchaser in the exercise of its reasonable business discretion relating to the development and commercialisation of a Gene Therapy Product owned by it or to which it has exclusive rights, with similar product characteristics as the relevant Programme or Royalty Product, which is of similar market potential at a similar stage in its development or product life as the relevant Programme or Royalty Product, taking into account issues of scientific risk, patent coverage, safety and efficacy, product profile, the competitiveness of the marketplace, the proprietary position, the regulatory structure involved and profitability (including pricing and reimbursement status achieved or likely to be achieved) and other relevant factors, including without limitation, technical, legal, scientific and/or medical factors**;**

"**Completion**" means completion of the sale and purchase of the Assets in accordance with clause 4;

"**Completion Date**" means 5:30pm in the UK on the date of this Agreement;

"**Confidential Information**" means all information held in any form or media whatsoever which is of a confidential nature and not in the public domain;

"**Consent**" means a consent, licence, approval, authorisation or waiver from the relevant counterparties to a Business Contract for the benefit and burden of such contract to be conveyed, transferred, assigned or novated to the Purchaser;

"**Consent Contracts**" means those contracts which require Consent, being:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***];

(f) [***];

(g) [***]; and

(h) [***];

"**Consideration**" means the sum of the Initial Consideration and the Additional Consideration (if any);

"**Consideration Shares**" means the 15,563,230 fully paid Series B2 Convertible Preferred Shares of £0.00001 each in the capital of the Purchaser; which the parties agree shall be issued at a price of £4.019 per share;

"**Control**" means:

(i) with respect to any partnership, corporation or other entity, the right to control or cast a majority of the voting rights exercisable at a shareholders meeting (or its equivalent) of the person concerned; or the right to appoint or remove directors having a majority of the voting rights exercisable at meetings of the board of directors and/or any supervisory board of the person concerned (or its equivalent); or the possession directly or indirectly of the ability or power to direct or procure the direction of the management and policies of such person, whether through the ownership of securities, by contract or otherwise; and

(ii) with respect to any material, item of information or Intellectual Property, the possession, whether by ownership or licence, of the right to grant a licence or a sublicence with respect thereto or to disclose relevant information relating thereto without breaching any prior written obligation to any third party.

The term "**Controlled**" shall be construed accordingly;

"**Core IP**" means (a) any Licensed Know-How or Patient-Level Clinical Data; or (b) any Arising Programme IP;

"**Cumulative**" means, when used in conjunction with Net Sales in this Agreement, that all aggregate Net Sales (regardless of when such sales occurred) shall be taken into account when determining the total amount of Net Sales of the applicable Royalty Product for the purposes of determining the amount of any royalty payment or milestone payment hereunder;

"**Damages Payment**" has the meaning defined in Schedule 6;

"**Data Processing Agreement**" means the data processing agreement between the Seller and the Purchaser dated the Completion Date;

"**Data Room**" means the collection of documents, information and materials on two identical USB drives marked "[***] – Disclosure Documents";

"**Default Rate**" means [***] above the base rate from time to time of the Bank of England;

"**Defaulting Party**" has the meaning defined in clause 25.1;

"**Deferment Notice**" has the meaning defined in clause 5.3(g);

"**Disclosure Letter**" means the letter dated the Completion Date from the Seller to the Purchaser with respect to the Warranties;

"**Dispute**" means a dispute between the parties under, arising out of, or in connection with this Agreement, including any question regarding its existence, validity or termination;

"**Encumbrance**" means any mortgage, charge, claim, lien, option, power of sale, hypothecation, or any other third party right, retention of title, right of pre-emption, right of refusal or security interest of any kind;

"**EU**" means all economic, scientific and political organisation of member states known as the European Union, as its membership may be altered from time to time, and any successor thereto. For clarity, the United Kingdom shall be considered as part of the EU in all situations for all purposes for the entire duration of this Agreement;

"**Excluded Assets**" means any assets or other property of the Seller or its Affiliates other than the Assets;

"**Expert**" means an expert appointed in accordance with clause 32.2;

"**FDA**" means the United States Food and Drug Administration and any successor body thereto;

"**FDA Approval**" means the approval by the FDA of an MAA for the marketing and sale of Strimvelis, an MLD Royalty Product, a WAS Royalty Product or a Beta-Thal Royalty Product, respectively, in the USA;

"**Field**" means any of the following: (i) non-clinical in vivo studies aimed at developing a Gene Therapy Product; (ii) clinical development of a Gene Therapy Product; or (iii) commercial development of a Gene Therapy Product; in each case where such studies, development or commercial activity is for the purpose of developing a Gene Therapy Product for the treatment of any disease, disorder or condition in an Indication which, as at the Completion Date, is the subject of any Programme;

"**First Commercial Sale**" means with respect to each Royalty Product, the first sale for which revenue has been recognised by a party, its Affiliates, licensee or sublicensee provided, that, the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate, licensee or sublicensee unless the Affiliate, licensee or sublicensee is the last entity in the distribution chain of a Royalty Product, (b) any sale for use of such Royalty Product in pre-clinical research, clinical studies or other development activities conducted in part for the purpose of seeking an MAA for such Royalty Product, (c) disposal or transfer of such Royalty Product for a bona fide charitable purpose, and (d) compassionate use sales, or use or sales under other equivalent systems (including for the avoidance of doubt any early access programmes);

"**Forum Meetings**" has the meaning defined in clause 11.3;

"Fundamental Claims"

(a) as applied to the Seller: any Claim relating to (i) [***]; (ii) [***]; and/or (iii) [***]; and/or (v) [***];

(b) as applied to the Purchaser: any Claim relating to (i) [***]; (ii) [***]; (ii) [***]; (iii) [***];

"**Gene Therapy Product**" means the administration of genetic material to modify or manipulate the expression of gene product or to alter the biological properties of living cells for therapeutic use;

"**Governmental Entity**" means any government or governmental or regulatory body thereof, or political subdivision thereof, whether supranational, national, federal, state, regional, local, foreign or other governmental or non-governmental department, commission, tribunal, authority, agency or court or any other agency or instrumentality thereof;

"**GSK Programme**" means a development programme carried on by or for the Seller or its Affiliate (which shall, in respect of academic partners, include a development programme carried on in collaboration with the Seller or its Affiliate), or a product being developed or commercialised by the Seller or its Affiliate, or a programme for which the Seller or its Affiliate has a right to obtain an exclusive licence;

"**GSK Stable Cell Line**" means the patent application referenced as international application number [***], or [***] and [***], including without limitation any certificates of invention, non-provisional patent applications, paediatric use extensions, substitutions, divisionals, continuations, continuations-in-part, reissues, reexaminations, renewals, confirmations, extensions and supplementary protection certificates, and any equivalent rights granted in any foreign jurisdictions, any Know-How included therein and the Beta Globin transgene (provided that the Beta Globin transgene is included in the GSK Stable Cell Line for the sole purpose of conducting research activities);

"**Human Biological Samples**" means any human biological material (including any derivative or progeny thereof), including any portion of an organ, any tissue, skin, bone, muscle, connective tissue, blood, cerebrospinal fluid, cells, gametes, or sub-cellular structures such as DNA, or any derivative of such biological material such as stem cells or cell lines; and including any Patient Samples provided to the Purchaser under this Agreement or the Transition Services Agreement;

"**Independent Third Party**" means a person other than the Purchaser or any of its Affiliates, distributors or licensees, or a person other than the Seller or any of its Affiliates, distributors or licensees, as the case may be;

"**Indication**" means a disease, treatment area or therapeutic indication;

"**Initial Consideration**" means the sum of the (i) Initial Payment and (ii) Consideration Shares;

"**Initial Payment**" means the sum of £10,000,000;

"**Intellectual Property**" means rights in information, patents, patent applications (filed and unfiled), inventions, invention disclosures, invention assignments, design rights, copyrights and other works of authorship (including rights in computer software), rights in databases, rights in Know-How, utility models, trademarks, trade dress, logos, slogans, rights of publicity, service marks, service names, web addresses, domain names, trade and business names and all associated goodwill, rights to sue for passing off or for unfair competition and all other similar or equivalent rights in any part of the world, in each case whether registered or unregistered and including all applications for, and renewals or extensions of, such rights for their full term;

"**Inventory**" means inventory which is owned by the Seller and/or its Affiliates as at the Completion Date ([***]) which the Purchaser or its Affiliates has agreed to acquire pursuant to the Inventory Sale Agreement(s);

"**Inventory Sale Agreement(s)**" means the Inventory Sale Agreement(s) between the Seller and the Purchaser dated the Completion Date in the form set out in Schedule 2;

"**IPO**" means the admission to trading of any shares of the Purchaser (or any holding company of the Purchaser), or granting of permission for any such shares to be dealt on, a Recognised Investment Exchange or other stock exchange;

"**Joint Transition Committee**" or "**JTC**" has the meaning defined in clause 17.1;

"**Know-How**" means all information, techniques, technology, practices, trade secrets, inventions (whether patentable or not), methods, knowledge, know-how, results, analytical methods, data, instructions, processes, procedures, formulas and other confidential and proprietary information and practices;

"[***] **Licence Agreement"** means the [***] Agreement [***] between [***] and GSK IPD [***];

"**Licences**" means the licences granted by the Seller to the Purchaser pursuant to clause 2.2;

"**Licensed Know-How**" means the following Know-How that is owned by or licensed to the Seller (and its Affiliates):

(a) the Clinical Data;

(b) the Production Information;

(c) the CMC Know-How; and

(d) to the extent the Seller or any of its Affiliates is entitled to sub-licence the same, any Know-How licensed to the Seller or its Affiliates pursuant to the Business Contracts;

"**Losses**" includes, in respect of any matter, event or circumstance, all demands, claims, actions, proceedings, damages, payments, awards, fines, penalties, losses, costs (including without limitation amounts paid in settlement, costs of investigation and legal costs), expenses (including taxation), disbursements or other liabilities in any case of any nature whatsoever but which shall exclude (a) indirect loss of profit and which are, where relevant, paid in accordance with the terms of this Agreement and (b) VAT which is recoverable (by way of payment, set off or credit) by the party claiming the Losses;

"**MAA**" means (a) a marketing authorisation application filed with the European Medicines Agency, seeking product registration of a product and all variations thereto filed with the European Medicines Agency; (b) a new drug application or biologics licence application submitted to the FDA; or (c) a corresponding application for product registration that has been submitted to a Regulatory Authority in any other jurisdiction in the Territory;

"**Material CRE Breach**" has the meaning defined in clause 20.1;

"**Milestone Report**" has the meaning defined in clause 5.3(h)(ii);

"**MLD Programme**" means the gene therapy research, development and commercialisation programme with respect to Metachromatic Leukodystrophy that was conducted prior to Completion by Telethon-HSR or Seller and its Affiliates and following Completion such programme that continues to be conducted by Purchaser and its Affiliates and/or their licensees and assignees utilising, inter alia, the Assets, the Patient-Level Clinical Data or the Licensed Know-How;

"**MolMed Agreement**" means the Amended and Restated Strategic Manufacturing Collaboration Agreement dated 1 September 2016 between GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline Trading Services Limited and MolMed S.p.A. for certain manufacturing and cell processing activities for the Programmes;

"**Net Sales**" means, with respect to any Royalty Product, the amounts actually received and recorded in the Purchaser's accounts in respect of sales of such Royalty Product sold by the Purchaser or its Affiliates or sub-licensees (the "**Selling Party**"), but [***] as reported by the Selling Party in its financial statements in accordance with the International Financial Reporting Standards ("**IFRS**") for the Purchaser (or any other Selling Party which accounts in accordance with IFRS) applied on a consistent basis, for:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***]; and

(f) [***].

Sales between the Purchaser and its Affiliates or sub-licensees, as applicable, shall be excluded from the computation of Net Sales, and no payments will be payable on such sales except where such Affiliate or sub-licensee is the end user in the distribution chain for a Royalty Product, in which case such sales shall be deemed to be at a price which is equivalent to the price which would normally be charged on an arms' length basis for equivalent sales.

For purposes of determining royalties and sales milestones payable on Combination Products, Net Sales will be calculated as follows, in each Calendar Quarter:

If a Royalty Product is sold as part of a Combination Product (as defined below), Net Sales will be the product of (i) Net Sales of the Combination Product calculated as above (i.e., calculated as for a non-Combination Product) and (ii) the fraction (A/(A+B)), where:

A is [***]; and

B is [***].

If A or B cannot be determined by reference to Royalty Product sales as described above, then Net Sales for purposes of determining royalty payments will be calculated as above, but the average wholesale acquisition cost in the above equation shall be determined by mutual agreement reached in good faith by the parties prior to the end of the accounting period in question based on an equitable method of determining same that takes into account, in the applicable country, variations in dosage units and the relative fair market value of each therapeutically active ingredient in the Combination Product. If the parties are unable to reach such an agreement prior to the end of the applicable accounting period, then either party may refer such matter to an independent certified accountant in accordance with clause 13.2.

Where a Royalty Product is sold and part of the amounts received in respect of that sale are contingent, refundable, payable in instalments or repayable after the date of receipt, including in relation to clinical outcomes of the use of the relevant Royalty Product, then the Net Sales shall apply: (i) to the non-contingent, non-refundable component of the amount on the date of receipt and those instalments where cash has actually been received and recorded in the Purchaser's accounts: and (ii) in respect of any contingent, instalment or refundable amount on the date on which it ceases to be deferred, contingent or refundable, or in the case of instalment payments, in the period when the instalment is actually received and recorded and recorded in the Purchaser's accounts;

"**Notice**" has the meaning defined in clause 26.1;

"**Novated Contracts**" means the contracts listed in Schedule 1 of the Telethon Deed of Novation;

"**Opportunity Period**" has the meaning defined in clause 10.2(a);

"**Other Party**" means a party or its Affiliate against which a Claimant brings a claim;

"**Other Safety Concern**" means any event arising out of a Programme with respect to a Royalty Product, where such event, is not a Significant Safety Concern but causes the Purchaser, acting reasonably as demonstrated by evidence provided by the Purchaser to the Seller, to determine that continuing to treat patients in the Programme would be unsafe (taking into account the benefits to the patients being treated);

"**Other Seller IP**" means any Intellectual Property (which is not Licensed Know-How, Patient-Level Clinical Data or which relates to the Seller Stable Cell Line) generated and Controlled by the Seller and/or its Affiliates before the Completion Date or that is generated from time to time up to and including the TSA Expiration Date which was used by the Seller or its Affiliates and utilised in the Programmes;

"**OTL-101**" means the ex-vivo lentiviral gene therapy product developed by the Purchaser for the treatment of ADA-SCID currently designated as OTL-101;

"**Patient-Level Clinical Data**" means, to the extent in existence at the Completion Date or that is generated from time to time up to and including the TSA Expiration Date and in the Control of the Seller, its Affiliates or subcontractors, the anonymized patient-level data arising in the clinical studies for Strimvelis and the Programmes as maintained by:

(a) [***]; and

(b) [***],

in each case, in the form in which it is held by or on behalf of the Seller or its Affiliates;

"**Patient Samples**" means, to the extent in existence at the Completion Date and in the control of the Seller, the anonymized patient-level physical samples arising in the clinical studies for Strimvelis and the Programmes;

"Proceedings" means any suit, action or proceedings arising out of, or in connection with this Agreement;

"**Product Registrations**" means the registration of a product with any competent Governmental Entity, including any granted MAA and, with respect to Strimvelis as at the Completion Date, means those that are listed in the Regulatory Information. As of the Completion Date, the Strimvelis Product Registration is the only Product Registration in existence;

"**Production Information**" means, to the extent in existence at the Completion Date or that is generated from time to time up to and including the TSA Expiration Date, the information which is owned by, and in the possession of, the Seller or any of its Affiliates which is listed in Exhibit 3 (in the form in which it is held by the Seller);

"**Programme**" means the ADA-SCID Programme, the WAS Programme, the MLD Programme, the Beta-Thal/Sickle Cell Programme and the Unoptioned Programmes (or any of them as the context may require);

"**Programme Transfer Plan**" means the plan attached hereto as Schedule 10;

"**Purchaser Accounts Receivable**" means:

(a) all amounts owing to the Purchaser and/or its Affiliates, as the case may be, exclusively in connection with the Programmes as at, and in respect of the period after, the Completion Date; and

(b) all amounts in respect of sales of Strimvelis where title has transferred from the Purchaser or its Affiliates to a third party purchaser after the Completion Date, whether or not invoiced;

"**Purchaser Demands**" has the meaning defined in clause 7.3;

"Purchaser Platform IP" means any Intellectual Property generated and Controlled by the Purchaser and its Affiliates after the Completion Date which is applicable to Gene Therapy Product programmes generally and is not Arising Programme IP;

"**Purchaser Programmes**" means, other than the Programmes, the Purchaser's research, development and commercialisation programmes with respect to ex-vivo gene therapies which are independently derived by Purchaser;

"**Purchaser Protected Parties**" means the Purchaser and its Affiliates;

"**Purchaser Relevant Affiliate**" has the meaning defined in clause 15.5(a);

"**Recognised Investment Exchange**" means a recognised investment exchange as defined by section 285 of the Financial Services and Markets Act 2000 and every statutory modification or re-enactment thereof for the time being in force, together with (whether or not falling within such definition) the Official List of the UK Listing Authority, the Main Market of the London Stock Exchange plc, the AIM market of the London Stock Exchange plc and NASDAQ;

"**Regulatory Authority**" means, with respect to a pharmaceutical or medicinal product, in any particular jurisdiction, any country, federal, supranational, state or local regulatory agency, department, bureau or other Governmental Entity or regulatory authority in such jurisdiction that has responsibility for granting a Product Registration for a pharmaceutical or medicinal product in such jurisdiction, in each case together with any successor(s) thereto;

"**Regulatory Information**" means, to the extent in existence at the Completion Date or that is generated from time to time up to and including the TSA Expiration Date and in the Control of the Seller, the information which is listed in Exhibit 4 in the form in which it is held by or on behalf of the Seller:

"**Report Acceptance Date**" has the meaning defined in clause 5.3(h)(iii);

"**Requested Information**" means reasonable business, financial and other information regarding the Seller and its Affiliates (in each case, where applicable, in accordance with IFRS);

"**Retained Liabilities**" has the meaning defined in clause 7.2;

"**Right**" has the meaning defined in clause 23.2;

"**Royalty Product**" means all or any of the following:

(a) Strimvelis and/or OTL 101 (an "**ADA-SCID Royalty Product**");

(b) a Therapeutic Product developed pursuant to the WAS Programme (a "**WAS Royalty Product**");

(c) a Therapeutic Product developed pursuant to the MLD Programme (a "**MLD Royalty Product**"); and

(d) a Therapeutic Product developed pursuant to the Beta-Thal/Sickle Cell Programme (a "**Beta-Thal Royalty Product**");

"**Royalty Reports**" has the meaning defined in clause 5.3(h)(i);

"**Royalty Term**" the period commencing on the Completion Date and ending thirty (30) years from the Completion Date;

"**Safety Data Exchange Agreement**" means the safety data exchange agreement between the Purchaser and the Seller dated the Completion Date;

"**Sale PRV**" means a priority review voucher obtained by the Purchaser in connection with the FDA Approval of a Royalty Product (excluding for these purposes any PRV obtained in connection with OTL-101);

"**SCID Compassionate Use Patients**" means up to [***] patients to be treated at San Raffaele Hospital with the Gene Therapy Product treatment commercially licensed in Europe under the name Strimvelis, using mobilized peripheral blood, in an investigator sponsored study or under a compassionate use regulatory framework in Italy, as agreed between the Seller and the San Raffaele Hospital prior to the Completion Date;

"SCID Compassionate Use Vector Inventory" means the amount of inventory of vector used to manufacture Strimvelis sufficient to treat the SCID Compassionate Use Patients, and which is provided by the Seller at no cost to the Purchaser pursuant to the Inventory Sale Agreement, such SCID Compassionate Use Vector Inventory to be utilised by the Purchaser for the purposes of treating the SCID Compassionate Use Patients;

"**Seller Accounts Receivable**" means all amounts in respect of sales of Strimvelis where title has transferred from the Seller or its Affiliates to a third party purchaser after the Completion Date, whether or not invoiced;

"**Seller Affiliate**" has the meaning defined in clause 10.2;

"**Seller Demands**" has the meaning defined in clause 7.4;

"**Seller Protected Parties**" means the Seller and its Affiliates;

"**Seller Required Asset(s)**" has the meaning defined in clause 19.1;

"**Seller's Marks**" means any trade or service marks, trade or service names or logos used or held by the Seller and/or any of its Affiliates or any confusingly similar mark, name or logo;

"**Senior Managers**" means with respect to the Seller, a Senior Vice President, Worldwide Business Development, and with respect to the Purchaser, its CEO;

"**Shareholder Documents**" means: (i) the agreed form subscription letter in respect of the Consideration Shares (ii) the agreed form deed of adherence to the investment and shareholders' agreement relating to the Purchaser dated 29 March 2017 (as amended on 18 August 2017 and 26 October 2017) and (iii) the agreed form variation agreement relating to the investment and shareholders' agreement;

"**Significant Safety Concern**" means any serious adverse event, laboratory finding or clinical syndrome that occurs with respect to (i) any patient(s) participating in a clinical study with respect to a Royalty Product that causes the data safety monitoring board (DSMB) for such study to recommend or require (as the case may be) that the study be terminated; or (ii) any patient receiving treatment involving a Royalty Product that causes any Regulatory Authority to recommend or require (as the case may be) that the study be terminated;

"**Strimvelis**" means the Seller's Gene Therapy Product for ADA-SCID sold under the brand name Strimvelis®;

"**Supply Chain Transfer Date**" has the meaning defined in the Transition Services Agreement;

"**Tax**" or "**Taxation**" means all forms of taxation and all withholdings, duties, imposts, levies, social security contributions and rates imposed, assessed or enforced by any Tax Authority in all cases being in the nature of taxation and any interest, penalty, surcharge or fine in connection therewith;

"**Tax Authority**" means any local, municipal, governmental, supranational, national, state, federal, provincial or other fiscal, revenue, customs or excise authority, body or official anywhere in the world;

"**Tax Warranty Claim**" means any Warranty Claim in respect of the warranties set out in Schedule 5, paragraphs 10.1 to 10.10 (inclusive);

"**Telethon Deed of Novation**" means the deed of novation dated on or around the date of this Agreement entered into by the Seller and certain of its Affiliates, the Purchaser, Telethon and HSR relating to the novation of certain agreements (including the Telethon-HSR Agreement) pursuant to which the Purchaser has agreed to assume the rights and obligations of the Seller and/or its Affiliates under such agreements;

"**Telethon-HSR Agreement**" means the Research and Development Collaboration and License Agreement dated 15 October 2010 between Telethon, HSR and Glaxo Group Limited (as amended by amendment agreements dated 31 March 2015, 4 April 2016, 23 September 2016, 15 December 2016 and 15 July 2017), relating to a collaboration between the parties for the research, development and commercialisation of certain rare disease gene therapy programmes;

"**Testing Period**" means each consecutive [***] period (commencing on any date and ending on any date) within the prior [***] period;

"**Transition Services Agreement**" means the transition services agreement between the Seller and the Purchaser dated the Completion Date;

"**Territory**" means worldwide;

"**Therapeutic Product**" means a Gene Therapy Product which is intended for use in connection with: (i) preventing, diagnosing, caring or alleviating a disease, ailment, defect or injury in persons; or (ii) influencing, inhibiting or modifying a physiological process in persons;

"**Third Party Claim**" has the meaning defined in Schedule 6;

"**Trademark and Domain Name Assignment Agreement**" means the trademark and domain name assignment agreement between the Seller and the Purchaser dated the Completion Date;

"**Transaction Documents**" means this Agreement, the Disclosure Letter, the Transition Services Agreement, the Safety Data Exchange Agreement, the Inventory Sale Agreement, the Data Processing Agreement and the Trademark and Domain Name Assignment Agreement;

"**Transfer Regulations**" means any laws of any jurisdiction relating to the safeguarding of employees' rights in the event of transfers of undertakings, businesses or parts of undertakings or businesses as amended or replaced from time to time including any such laws implementing Council Directive 2001/23/EC;

"**TSA Expiration Date**" means the date that the Transition Services Agreement terminates or is terminated or, if earlier, the expiry of the last Service Term (as defined in the Transition Services Agreement);

"**Undisclosed Employee**" has the meaning as defined in clause 10.2;

"**Unexecuted Contracts**" means:

(a) the [***]; and

(b) the [***];

"**Unoptioned Programmes**" means the following research, development and commercialisation programmes conducted prior to Completion and following Completion by Telethon-HSR under the Telethon-HSR Agreement, and in respect of which the option granted by Telethon-HSR to the Seller thereunder has not been exercised as at the Completion Date: (i) Chronic granulomatous Disease; (ii) Globoid cell leukodystrophy; and (iii) Mucopolysaccaridosis Type I (Hurler);

"**USA**" means the United States of America;

"**Valid Claim**" means a claim within an issued patent that has not:

(a) expired, lapsed or been finally cancelled or abandoned, been dedicated to the public or disclaimed; or

(b) been held unenforceable, invalid or permanently cancelled by a court or administrative agency of competent jurisdiction in an order or decision from which no appeal can be taken or from which no appeal was taken in the time permitted, including through opposition, re-examination, reissue or disclaimer;

"**VAT**" means the tax imposed by the Council Directive 2006/112/EC of the European Community and any national legislation implementing that directive together with legislation supplemental thereto, or other tax of a similar nature, including sales taxes imposed elsewhere instead of or in addition to value added tax;

"**Warranties**" means the warranties given by the Seller in clause 15 and Schedule 5;

"**Warranty Claim**" means any claim by the Purchaser or any Affiliate of the Purchaser against the Seller for breach of the Seller's Warranties;

"**WAS Programme**" means the gene therapy research, development and commercialisation programme with respect to WAS that was conducted prior to Completion by Telethon-HSR, the Seller and its Affiliates and following Completion such programme that continues to be conducted by the Purchaser and its Affiliates and/or their licensees and assignees utilizing, inter alia, the Assets, the Patient-Level Clinical Data or the Licensed Know-How; and

"WAS Vector ISS Inventory" means the inventory of vectors relating to the WAS Programme which the Seller has agreed to sell to [***] being the investigator undertaking the investigator sponsored study [***], in accordance with the agreement between the Seller and such investigator.

1.2 Statutory provisions

All references to statutes, statutory provisions, enactments, EU Directives or EU Regulations shall include references to any consolidation, re-enactment, modification or replacement of the same, any statute, statutory provision, enactment, EU Directive or EU Regulation of which it is a consolidation, re-enactment, modification or replacement and any subordinate legislation in force under any of the same from time to time except to the extent that any consolidation, re-enactment, modification or replacement enacted after the date of this Agreement would extend or increase the liability of any party to the other under this Agreement.

1.3 Agreed form

Any reference to a document in the "**agreed form**" is to the form of the relevant document in the terms agreed between the Seller and the Purchaser prior to the execution of this Agreement and signed or initialled for identification purposes only by or on behalf of the Seller and the Purchaser (in each case with such amendments as may be agreed by or on behalf of the Seller and the Purchaser).

1.4 Recitals, Schedules, Exhibits etc.

References to this Agreement include the recitals, schedules and exhibits which form part of this Agreement for all purposes. References in this Agreement to the parties, the recitals, schedules, exhibits and clauses are references respectively to the parties and their legal personal representatives, successors and permitted assigns, the recitals, schedules and exhibits to and clauses of this Agreement.

1.5 Meaning of references

Save where specifically required or indicated otherwise:

(a) words importing one gender shall be treated as importing any gender, words importing individuals shall be treated as importing corporations and vice versa, words importing the singular shall be treated as importing the plural and vice versa, and words importing the whole shall be treated as including a reference to any part thereof;

(b) references to a "**person**" shall include any individual, firm, body corporate, unincorporated association, government, state or agency of state, association, joint venture or partnership, in each case whether or not having a separate legal personality. References to a company shall be construed so as to include any company, corporation or other body corporate wherever and however incorporated or established;

(c) references to the word "**include**" or "**including**" (or any similar term) are not to be construed as implying any limitation and general words introduced by the word "**other**" (or any similar term) shall not be given a restrictive meaning by reason of the fact that they are preceded by words indicating a particular class of acts, matters or things;

(d) references to any English statutory provision or legal term for any action, remedy, method of judicial proceeding, legal document, legal status, court, official or other legal concept, state of affairs or thing shall in respect of any jurisdiction other than England be deemed to include that which most nearly approximates in that jurisdiction to the English statutory provision or legal term or other legal concept, state of affairs or thing;

(e) any reference to "**writing**" or "**written**" includes any method of reproducing words or text in a legible and non-transitory form but, for the avoidance of doubt, shall not include e-mail;

(f) references to "**£**" or "**GBP**" are to the lawful currency of the United Kingdom as at the date of this Agreement; and

(g) references to times of the day are to that time in London and references to a day are to a period of 24 hours running from midnight to midnight.

1.6 Headings

Clause and paragraph headings and the table of contents are inserted for ease of reference only and shall not affect construction.

2. SALE AND PURCHASE OF ASSETS AND GRANT OF LICENCES

2.1 Sale and Purchase of Assets

The Seller shall sell or procure to be sold to the Purchaser and the Purchaser shall purchase from the Seller, with effect from the Completion Date, the Seller's entire legal and beneficial interest in the following assets ("**Assets**"):

(a) subject to clause 9, the benefit and the burden of the Business Contracts;

(b) the Business Intellectual Property (which shall be transferred subject to and in accordance with the terms of clause 11);

(c) the Product Registrations (which shall be transferred subject to and in accordance with the terms of clause 5.2(a));

(d) the Commercial Information;

(e) the Cassette-Insert for each Programme; and

(f) the Regulatory Information.

The Seller covenants with the Purchaser that it has the right to sell and transfer to the Purchaser the full legal and beneficial interest in the Assets to be sold by it on the terms set out in this Agreement. The Assets shall be sold free from all Encumbrances but subject to the third party rights under the Business Contracts.

2.2 Grant of Licences

The Seller grants to the Purchaser, with effect from the Completion Date, licences on the terms set out in clause 11.2.

2.3 Inventory

The Seller and Purchaser have entered into the Inventory Sale Agreement on Completion for the purchase of the Inventory.

2.4 Assets excluded from Sale

There shall be excluded from the sale and purchase under this Agreement (and accordingly nothing in this Agreement shall operate as a sale from the Seller or any of its Affiliates) of any Excluded Assets. Except as expressly provided in this Agreement or in a Transaction Document, nothing in this Agreement will be construed as conferring to the Purchaser any licence or other right or interest, by implication, estoppel or otherwise, in any Intellectual Property right of the Seller, its Affiliates, or its collaboration partners.

2.5 Sale of the Assets

Neither party shall be obliged to complete the sale and purchase of the Assets unless the grant of the Licences and the sale and purchase of the Assets is completed simultaneously in accordance with this Agreement, provided that the necessity of the consent of any person, or any filing with or approval of any Governmental Entity to effect the effective transfer of any Product Registration, Business Contract or Business Intellectual Property shall not prevent simultaneity of Completion in accordance with this clause 2.5.

2.6 Title

Title to those Assets transferred at Completion shall pass to the Purchaser on Completion.

3. CONSIDERATION

3.1 Total consideration

The total consideration for the sale and transfer of the Assets to be paid by the Purchaser to the Seller is the Initial Consideration.

The total consideration for the Licences to be paid by the Purchaser to the Seller is the Additional Consideration.

3.2 Payment for and Delivery of Inventory

The amount payable by the Purchaser or its Affiliates in respect of the Inventory shall be calculated and paid as set out in the Inventory Sale Agreement.

3.3 Timing of Payment

(a) The Purchaser shall pay the Initial Payment within thirty (30) days of Completion, and issue the Consideration Shares to the Seller at Completion, in accordance with clause 4.4.

(b) The Additional Consideration, if any, shall become due and payable by the Purchaser to the Seller in accordance with the provisions of clause 5.3(j).

4. COMPLETION

4.1 Timing

Completion shall take place on the Completion Date.

4.2 Location

Completion shall take place at the offices of King & Spalding International LLP, 125 Old Broad Street, London, EC2N 1AR when all (but not some only) of the events detailed in this clause 4 shall occur.

4.3 Seller's obligations at Completion

At Completion, the Seller shall do (or cause to be done) or deliver (or cause to be delivered) to the Purchaser the matters or items listed in part 1 of Schedule 3.

4.4 Purchaser's obligations at Completion

At Completion, the Purchaser shall do (or cause to be done) or deliver (or cause to be delivered) to the Seller the matters or items listed in part 2 of Schedule 3.

4.5 Obligation to complete

Neither the Purchaser nor the Seller shall be required to complete the transactions contemplated by this Agreement unless the other complies with its obligations under clause 4.3 or clause 4.4 (as the case may be).

4.6 Failure to complete

If either the Seller or the Purchaser fails to comply with its obligations under clause 4.3 or clause 4.4 (as the case may be) on the Completion Date, the non-defaulting party may (at its absolute discretion):

(a) defer Completion to a date not more than [***] after the Completion Date (such that the provisions of this clause 4 shall apply to Completion as so deferred); or

(b) terminate this Agreement by giving notice to the defaulting party in writing.

5. POST-COMPLETION OBLIGATIONS

5.1 Obligations of the Seller

(a) The Seller undertakes to the Purchaser to procure the performance and observance of those matters listed in Schedule 4, and in all other provisions of this Agreement requiring the performance or observance of any matter by the Seller after Completion.

(b) The Seller undertakes to the Purchaser to procure that it shall at the cost of the Seller:

(i) in accordance with the Programme Transfer Plan, submit the required filings, form or application required to be submitted by it to transfer the Product Registrations to the Purchaser; and

(ii) take such actions as are reasonably necessary to ensure that the Product Registrations are transferred to the Purchaser in accordance with the Programme Transfer Plan.

(c) Following the Completion Date and for a period of [***] thereafter, the Seller shall use Commercially Reasonable Efforts (as defined in this clause 5.1(c) below) to provide to the Purchaser, upon the Purchaser's request and solely in connection with the Purchaser's filing of an IPO in the USA, the Requested Information (without any liability therefor) to the extent required to comply with applicable U.S. securities law; provided that the Purchaser acknowledges that the Seller is not required to provide to the Purchaser any specific Requested Information as, until such Requested Information is actually requested, the Seller cannot confirm whether such Requested Information exists, or exists in the form or manner in which it may (or may not) ultimately be requested from the applicable Regulatory Authorities. The Purchaser agrees to consult with the Seller in advance of filing for an IPO and to reasonably agree upon language in any filings and correspondence between the Purchaser and the regulatory authorities regarding the Requested Information, and will reasonably incorporate Seller's comments regarding any discussions or correspondence with the applicable regulatory authorities with respect to the Requested Information. For the purposes of this clause 5.1(c) "Commercially Reasonable Efforts" shall mean the provision by the Seller [***]. The Seller shall provide the aforementioned [***] of time within a reasonable period of time following the request from the Purchaser. In the event that the agreed-upon Requested Information cannot be compiled within the aforementioned [***], the Seller and the Purchaser shall discuss, in good faith, the steps necessary for the provision of the Requested Information, [***]

(d) The Seller will use reasonable efforts to conduct the activities allocated to the Seller as set forth in Schedule 1 to the Transition Services Agreement.

(e) The Seller shall promptly send any correspondence received from a Regulatory Authority ([***]) relating to a Programme to the Purchaser and in all circumstances will promptly consult with the Purchaser on the Seller's proposed response (if required). The Seller agrees to act in accordance with the Purchaser's reasonable instructions unless to do so would conflict with the Seller's obligations under the Product Registrations or applicable laws or regulations.

5.2 Obligations of the Purchaser

(a) Transfer of Product Registrations

The Purchaser undertakes to the Seller to procure that, as soon as reasonably practicable following the transfer of the Product Registrations, and in any event within [***] thereof, it shall (i) apply to vary any such existing Product Registrations to the extent necessary to remove all reference to any Seller's Marks from Strimvelis, in each case such application(s) to be made to the appropriate Regulatory Authority; and (ii) take all actions necessary or advisable to ensure that the variations to any such existing Product Registrations are obtained; and (iii) take such other actions as may be required to effect such transfer. Save to the extent any Losses are caused as a result of: (i) the Seller breaching its obligations set out in clause 5.1(b); or (ii) any act or omission by the Seller, or failure by the Seller to comply with the Purchaser's reasonable instructions, in respect of effecting the transfer of the Product Registrations, the Purchaser shall indemnify the Seller Protected Parties for any Losses incurred by the Seller Protected Parties arising directly from the Product Registrations remaining in the Seller's or its Affiliate's name during the period from Completion until the completion of the transfer of Product Registrations pursuant to this clause 5.2(a).

(b) Development, Commercialisation and Marketing of the WAS Royalty Product

(i) The Purchaser shall use its Best Endeavours to file an MAA for the WAS Royalty Product in the USA by the [***] anniversary of the Completion Date provided that the obligation to utilise Best Endeavours shall not include an obligation to initiate and/or conduct new clinical studies [***] in relation to the WAS Royalty Product if additional studies are required by any Regulatory Authority as a condition to approval. For the avoidance of doubt, once the Purchaser has filed an MAA for the WAS Royalty Product in the USA in accordance with this paragraph 5.2(b)(i), it shall have no further obligations pursuant to this paragraph;

(ii) The Purchaser shall use its Commercially Reasonable Efforts to file an MAA for the WAS Royalty Product in the EU. Following receipt of the applicable Product Registration for the WAS Royalty Product, the Purchaser shall use Commercially Reasonable Efforts to maintain the applicable Product Registration with respect to the WAS Royalty Product and to market, sell and promote the WAS Royalty Product for the duration of the Royalty Term; and

(iii) The obligations set forth in clause 5.2(b)(i) and 5.2(b)(ii) are separate from and in addition to any obligations of the Purchaser under the Telethon-HSR Agreement.

(c) Development, Commercialisation and Marketing of an MLD Royalty Product

(i) The Purchaser shall use its Best Endeavours to file an MAA for the MLD Royalty Product in at least one of either the EU or the USA by [***] provided that the obligation to utilise Best Endeavours and Commercially Reasonable Efforts shall not include an obligation to initiate or conduct new clinical studies ([***]) of the MLD Royalty Product if additional studies are required by any Regulatory Authority as a condition to the approval. For the avoidance of doubt, once the Purchaser has filed an MAA for the MLD Royalty Product in at least one of either the EU or the USA in accordance with this paragraph 5.2(c)(i), it shall have no further obligations pursuant to this paragraph;

(ii) The Purchaser shall use its Commercially Reasonable Efforts to file an MAA for the MLD Royalty Product in the other jurisdiction (being either the EU or the USA depending on where the application is filed pursuant to paragraph (i)) by [***]; and
(ii) Commercially Reasonable Efforts following receipt of the applicable Product Registration for the MLD Royalty Product to maintain the applicable Product Registration with respect to the MLD Royalty Product and to market, sell and promote the MLD Royalty Product for the duration of the Royalty Term provided that the obligation to utilise Commercially Reasonable Efforts shall not include an obligation to initiate and/or conduct new clinical studies ([***]) in relation to the MLD Royalty Product if additional studies are required by any Regulatory Authority as a condition to approval; and

(iii) The obligations set forth in clause 5.2(c)(i) and 5.2(c)(ii) are separate from and in addition to any obligations of the Purchaser under the Telethon-HSR Agreement.

(d) Development, Commercialisation and Marketing of the Beta-Thal Royalty Product

The Purchaser shall use its Commercially Reasonable Efforts to develop and file an MAA for the Beta-Thal Royalty Product. Following receipt of the applicable Product Registration for the Beta-Thal Royalty Product, the Purchaser shall use Commercially Reasonable Efforts to maintain the applicable Product Registration(s) with respect to such Beta-Thal Royalty Product and to market, sell and promote the Beta-Thal Royalty Product for the duration of the Royalty Term. The obligations set forth in this clause 5.2(d) are separate from and in addition to any obligations of the Purchaser under the Telethon-HSR Agreement.

5.3 Royalty and Milestone Payments

(a) General

In consideration for the licence of the Licensed Know-How, the Purchaser shall pay to the Seller, the following non-refundable royalties and milestone payments in the manner and at the rates set forth below. Royalties and milestone payments shall be calculated from the date of First Commercial Sale of a Royalty Product (save as expressly set out in this Agreement), and shall be calculated on a country-by-country and product-by-product basis.

Royalties may be deferred solely in accordance with the provisions of clause 5.3(g).

(b) Royalties owed on ADA-SCID Royalty Product

Subject to clause 5.3(f), the Purchaser shall pay to the Seller a [***] royalty on the combined annual Net Sales of ADA-SCID Royalty Products during the Royalty Term from the Completion Date.

(c) Royalties owed on the WAS Royalty Product

Subject to clause 5.3(f), the Purchaser shall pay to the Seller royalties in respect of the WAS Royalty Product at the following tiered royalty rates during the Royalty Term from the date of First Commercial Sale of the WAS Royalty Product:

Cumulative Net Sales of the WAS Royalty Product:	Applicable Royalty Rate (% of Net Sales):
On aggregate Cumulative Net Sales of the WAS Royalty Product less than or equal to [***]	[***]
On aggregate Cumulative Net Sales of the WAS Royalty Product greater than [***]	[***]

Example. For clarity, the royalties payable pursuant to clause 5.3(c) are intended to operate on a cumulative basis. This means, for example, that if aggregate Cumulative Net Sales of the WAS Royalty Product within the Royalty Term exceed [***], then the Purchaser will pay the Seller a royalty of [***] on all future sales of the WAS Royalty Product.

(d) Royalties and Milestones owed on the MLD Royalty Product

Subject to clause 5.3(f), the Purchaser shall pay to the Seller royalties in respect of the MLD Royalty Product at the following tiered royalty rates during the Royalty Term from the date of First Commercial Sale of the MLD Royalty Product:

Cumulative Net Sales of the MLD Royalty Product:	Applicable Royalty Rate (% of Net Sales):
On aggregate Cumulative Net Sales of the MLD Royalty Product less than or equal to [***]	[***]
On aggregate Cumulative Net Sales of the MLD Royalty Product greater than [***]	[***]

Example. For clarity, the royalties payable pursuant to clause 5.3(d) are intended to operate on a cumulative basis. This means, for example, that if aggregate Cumulative Net Sales of the MLD Royalty Product within the Royalty Term exceed [***], then the Purchaser will pay the Seller a royalty of [***] on all future sales of the MLD Royalty Product**.**

The Purchaser shall also pay to the Seller the following non-refundable milestone payments in respect of the MLD Royalty Product on achievement of the following milestones:

MLD Net Sales Milestone Event:	Milestone Payment
First year in which annual Net Sales of the MLD Royalty Product are greater than [***]	[***]
First year in which annual Net Sales of the MLD Royalty Product are greater than [***]	[***]

(e) Royalties and Milestones owed on the Beta-Thal Royalty Product

The Purchaser shall pay to the Seller royalties in respect of the Beta-Thal Royalty Product at the following tiered royalty rates during the Royalty Term from the date of First Commercial Sale of the Beta-Thal Royalty Product:

Annual Net Sales of the Beta-Thal Royalty Product:	Applicable Royalty Rate (% of Net Sales):
On aggregate annual Net Sales of the Beta-Thal Royalty Product less than or equal to [***]	[***]
On aggregate annual Net Sales of the Beta-Thal Royalty Product greater than [***] but less than or equal to [***]	[***]
On aggregate annual Net Sales of the Beta-Thal Royalty Product greater than [***]	[***]

Example. For clarity, the royalties payable pursuant to clause 5.3(e) are intended to operate on an incremental basis. This means, for example, that if annual Net Sales of the Beta-Thal Royalty Product in a given calendar year are [***] then the Purchaser will pay the Seller a royalty of [***] on the first [***] of Net Sales of the Beta-Thal Royalty Product, [***] on the next [***] of Net Sales of the Beta-Thal Royalty Product and [***] on the next [***] of Net Sales of the Beta-Thal Royalty Product making a total payment of [***].

The Purchaser shall also pay to the Seller the following non-refundable milestone payments on achievement of the following milestones with respect to the Beta-Thal Royalty Product:

Beta-Thal Net Sales Milestone Event:	Milestone Payment
First year in which annual Net Sales of the Beta-Thal Royalty Product are greater than [***]	[***]
First year in which annual Net Sales of the Beta-Thal Royalty Product are greater than [***]	[***]

(f) Biosimilar Competitive Product

(i) In the event that the market share of a Biosimilar Competitive Product to a particular Royalty Product is equal to or greater than [***] of the total market for the applicable product (as determined on a Biosimilar Region to Biosimilar Region and Royalty Product by Royalty Product basis) (the "**Product Market**"), as determined in accordance with 5.3(f)(ii) below, then the Purchaser's obligation to pay royalties to the Seller as set forth in this Agreement shall be reduced to [***] of the royalty payments that would have otherwise been due in the absence of such Biosimilar Competitive Product.

(ii) The parties agree that the Product Market shall be determined as follows:

(A) the Purchaser (acting reasonably) shall submit a written proposal to the Seller demonstrating how it has calculated the Product Market (the "**Product Market Proposal**"). If applicable, the Purchaser will include a proposal regarding the inclusion or exclusion of treatments provided under a compassionate use or equivalent program.

(B) within [***] of receiving the Product Market Proposal, the Seller shall confirm to the Purchaser in writing (with reasonable details if it rejects) whether it accepts or rejects the Product Market Proposal;

(C) if the Seller accepts the Product Market Proposal, then royalties shall be paid in respect of the relevant Royalty Product in accordance with clause 5.3(f)(i) above. If the Seller rejects the Product Market Proposal then the following provisions of this clause 5.3(f)(ii)(C) shall apply:

(i) the parties shall discuss and agree in good faith what, if any, amendments to the Product Market Proposal should be made.

(ii) If no agreement is reached (or no discussion takes place) within [***], then either the Seller or Purchaser may by notice to the other require an Expert be appointed in accordance with clause 32 to determine the Product Market.

(g) Deferred Royalty Payments

(i) The Purchaser shall have the option to defer royalty payments arising for WAS Royalty Products and MLD Royalty Products that are otherwise owed to the Seller under this Agreement, on such Royalty Product by such Royalty Product basis, for a period up to [***] from the date of the First Commercial Sale of each such Royalty Product only as set out in clause 5.3(g)(iv) to enable the Purchaser to prioritise its available capital to develop and exploit such MLD Royalty Product and WAS Royalty Product, as applicable, to the maximum extent possible. In the event the Purchaser wishes to exercise this deferment option it shall provide written notice on a Royalty Product by Royalty Product basis to the Seller on or prior to the date [***] following the First Commercial Sale of the relevant MLD Royalty Product or WAS Royalty Product (a "**Deferment Notice**").

(ii) Each Deferment Notice shall be accompanied by a written statement setting out sufficient information to demonstrate that such deferment is necessary and in the best interests of the development and commercialisation of the WAS Royalty Products or MLD Royalty Products (as appropriate) as demonstrated by supporting evidence provided by the Purchaser of its plans to build the necessary commercial (including manufacturing) infrastructure supporting the launch of such WAS Royalty Product or MLD Royalty Product. A Deferment Notice may only be rejected by the Seller if the Seller has reasonable grounds for determining that the deferment is not necessary for the building of the necessary commercial infrastructure as aforesaid for the WAS Royalty Product or the MLD Royalty Product (as appropriate). In such circumstances the Seller shall provide the Purchaser with details of its concerns in writing within [***] of the date of receipt of the relevant Deferment Notice. If the Seller objects to the deferment in accordance with this clause 5.3(g)(ii) the parties shall discuss in good faith, but in the event no agreement is reached within [***], then either the Seller or Purchaser may by notice to the other require an Expert be appointed in accordance with clause 32.2 to determine whether the Purchaser has satisfied its obligations under this clause 5.3(g) and to determine whether the Seller has acted reasonably in objecting to the Deferment Notice**.** The parties agree that:

(A) [***];

(B) [***].

(iii) Following receipt of a Deferment Notice, in the event that the Seller does not object to the Deferment Notice, or has objected to the Deferment Notice in accordance with paragraph (ii) of this clause 5.3(g) and the parties have subsequently agreed or the Expert has so determined, the payment of each royalty payment due in respect of the WAS Royalty Product or the MLD Royalty Product, as applicable, due with respect to Net Sales in the period of [***] from the date of the First Commercial Sale shall be deferred until the date [***] following the date on which each such royalty payment would otherwise have been payable in accordance with clauses 5.3(c) and 5.3(d).

(iv) Each such deferred royalty payment shall be due and payable in full on the date which is [***] following the date on which each such royalty payment would otherwise have been payable provided that the Purchaser may repay any or all amounts which have been deferred on the last day of any earlier [***] by giving written notice to the Seller on [***].

(v) At all times while the payment of any royalties are deferred, the Purchaser shall provide the Seller with [***] reports of Net Sales in respect of the WAS Royalty Product and/or the MLD Royalty Product (as appropriate) (as set forth in clause 5.3(h)(i) below) made during each [***] with a calculation of the royalties being deferred during such [***].

(vi) Deferred royalty payments shall carry an interest charge at the Default Rate from the date such royalties would otherwise have been due until the date of repayment of the royalties by the Purchaser.

(vii) For the avoidance of doubt, nothing set forth in this clause (g) shall be construed to grant the Purchaser any deferral of any royalty or other payments that the Purchaser may otherwise owe to a third party with respect to a Royalty Product, including without limitation any such amounts that may be owed by the Purchaser to Telethon-HSR.

(h) Royalty and Milestone Reports and Payment

(i) The Purchaser shall provide to the Seller a written report on a [***] basis showing on a Royalty Product-by-Royalty Product and country-by-country basis, for all Royalty Product sold in the Territory during the previous [***], the Net Sales and royalty payments due during that [***] ("**Royalty Reports**"). Royalty Reports shall be due on the [***] following the close of each [***] except that Royalty Reports for the [***] ending on [***] shall be due on the [***] day following the close of that [***]. Royalties shown to have accrued during the relevant [***] shall be due on the date such Royalty Report is due and shall be paid in accordance with clause 5.3 (j).

(ii) The Purchaser shall provide to the Seller a written report on a [***] basis showing on a Royalty Product-by-Royalty Product, for all Royalty Product sold in the Territory during the previous [***], the Net Sales and the milestone payments due during that [***] ("**Milestone Reports**"). Milestone Reports shall be due on the [***] day following the close of each [***]. Milestones shown to have accrued during the relevant [***] shall be due on the date such Milestone Report is due and shall be paid in accordance with clause 5.3(j).

(iii) Any Royalty Report or Milestone Report shall be deemed accepted by the Seller, if it does not deliver a notice of objection pursuant to clause 5.3(i) upon the expiration of the [***] period referred to in clause 5.3(i) ("**Report Acceptance Date**").

(i) Disputed Royalty Statement.

(i) If the Seller determines to dispute a Royalty Report or a Milestone Report, then Seller shall, within [***] after receipt of a Royalty Report or a Milestone Report, provide notice in writing to the Purchaser specifying in detail the reasons for such dispute;

(ii) if the Seller delivers a notice in accordance with clause 5.3(i) (i) the parties shall attempt in good faith, for a period of not less than twenty (20) Business Days following receipt by Purchaser of such notice, to resolve the dispute specified in the notice concerning the Royalty Report or Milestone Report;

(iii) if the parties are unable to resolve any dispute arising in connection with such Royalty Report or Milestone Report during the twenty (20) Business Day period referred to above, then at the request of either party, the matter may be referred to an independent certified public accountant for resolution for determination in accordance with clause 13.2. The date on which such determination is issued to the parties shall be the "**Determination Date**".

(j) Payment

Within [***] of the Report Acceptance Date or (where applicable) the Determination Date, the Seller shall provide the Purchaser with a valid VAT invoice for any relevant VAT properly chargeable in respect of the relevant royalty payment or milestone payment. Within [***] of receipt of such invoice, the Purchaser shall transfer to the Seller the relevant payment (if any) by wire transfer of immediately available funds, in GBP, to the account details set out in paragraph 2 of Schedule 4 or to such other account as the Seller may notify the Purchaser from time to time provided that, for the avoidance of doubt, if a royalty payment is deferred following provision of a Deferment Notice under clause 5.3(g)(i), no amount shall be payable by the Purchaser (including in respect of VAT) until the later of (i) [***] and (ii) [***].

(k) Non-Refundable

It is agreed by the parties that all royalty payments and milestone payments made under this Agreement are intended to be and shall be non-refundable. Notwithstanding the foregoing, a party may bring and/or enforce a claim, action, judgment or decision alleging or confirming that some or all royalty payments or milestone payments should be repaid, have been overpaid, were not payable, or any other analogous matter relating to the calculation and payment of such royalties and/or milestone payments (as the case may be).

(l) Patient Access

(i) Notwithstanding the Purchaser's development of OTL-101 (which the Seller acknowledges), the Purchaser shall use its Best Endeavours to maintain the Product Registrations in the EU for Strimvelis in existence as at the Completion Date (and shall apply to renew the Product Registration for Strimvelis no later than the fifth anniversary of the date of such Product Registration) and continue to make Strimvelis available at San Raffaele Hospital (which shall include taking such steps as are reasonably required to ensure that each eligible patient who is referred for treatment with Strimvelis may proceed to treatment in a timely manner) to all patients eligible for treatment for whom Strimvelis will be reimbursed (i) until such time that an alternative viable Gene Therapy Product which has received all required Product Registrations in the EU and is commercially available for patients in the EU; (ii) notwithstanding (i), at all times at the San Raffaele Hospital, provided it is administered to at least [***] patients in the immediately preceding Testing Period who are entitled to receive reimbursement for the provision of Strimvelis.

(ii) In respect of the price set for reimbursement of Strimvelis in the EU as at the Completion Date, [***].

(iii) [***].

Nothing set forth in this clause 5.3 (l) shall be construed as a waiver of any obligation assumed by the Purchaser under the Telethon-HSR Agreement.

(m) Further Obligations of the Purchaser

Further, the Purchaser undertakes to the Seller to procure the performance and observance of those matters listed in Schedule 4.

The Purchaser shall ensure that all transactions related to the Assets and the transactions contemplated by this Agreement are accurately recorded in all material respects on its books and records in accordance with the Purchaser's internal accounting practices and controls, which are reasonably designed to ensure that it maintains no off-the-books accounts.

5.4 Notification of Change of Control or IPO

The Purchaser shall notify the Seller in writing promptly following any Change of Control including brief details of the proposed transaction. For the avoidance of doubt, this obligation shall not require the Purchaser to obtain the prior consent of the Seller prior to any Change of Control.

5.5 Restrictions on Assignment

(a) The Purchaser shall not, prior to [***], subject to clause 5.5 (e) and the terms of the Telethon-HSR Agreement, terminate development or commercialisation activities, or terminate the licence under the Telethon-HSR Agreement, under or with respect to the WAS Programme, the MLD Programme and/or Strimvelis without the prior written consent of the Seller.

(b) Subject to clause 5.5 (e) and the terms of the Telethon-HSR Agreement, the Purchaser shall not prior to [***] licence or further assign, sell, or transfer the development and commercialisation of Strimvelis, any WAS Royalty Product or MLD Royalty Product or any of its rights pursuant to such products or rights or obligations pursuant to the WAS Programme, the MLD Programme, or the ADA-SCID Programme without the prior consent of the Seller, such consent not to be unreasonably withheld (for avoidance of doubt, the Seller may reasonably withhold consent if the Seller believes that the proposed licensee or assignee or purchaser would be unable to satisfactorily meet the obligations with respect to such Programme under this Agreement).

(c) Subject to the terms of the Telethon-HSR Agreement, the Purchaser may at any time sublicense or transfer rights for the Beta-Thal/Sickle Cell Programme.

(d) Following the [***] (and at any time with respect to the Beta-Thal/Sickle Cell Programme as provided in clause 5.5 (c)) and subject to the terms of the Telethon-HSR Agreement, the Purchaser may licence or transfer the development and commercialisation of Strimvelis, the WAS Royalty Product, the MLD Royalty Product, the Beta-Thal/Sickle Cell Programme or its rights and obligations with respect to the WAS Programme, the MLD Programme, Beta-Thal/Sickle Cell Programme or the ADA-SCID Programme, excluding for this purpose OTL-101 (each, an "**Assignment Transaction**") provided that:

(i) [***]; and

(ii) [***]

The Purchaser shall pay any amounts owing to the Seller pursuant to this clause 5.5(d)(ii) shall pay any amounts within [***] of the date such amount is actually received by the Purchaser or its Affiliate as the case may be.

For the purposes of this clause, pivotal study shall mean a clinical study that is undertaken on the number of patients recommended by the FDA or the European Medicines Agency (as the case may be) as sufficient to support a filing of an application for a MAA on the assumption that the primary end point of the clinical study is met and which study is in other material respects designed to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the relevant Programme.

(e) Notwithstanding clauses 5.5(a) to (d) and clause 30.1, the Purchaser may contract with suppliers, distributors, manufacturers, contract sales organisations, contract research organisations or other third parties in support of its activities pursuant to the Programmes, or enter into arrangements with a third party for the furtherance of its development activities pursuant to the Programmes, in each case without the prior consent of the Seller; provided that the Purchaser shall remain responsible for the performance of its obligations hereunder by any such third party and provided that the Seller's liability to the Purchaser shall not be greater than if such assignment had not taken place.

6. APPORTIONMENTS

6.1 Apportionment of periodical charges and outgoings

All periodical amounts paid or payable under any of the Business Contracts shall be apportioned on a time basis so that such part of the relevant charges and outgoings as is attributable to the period ended on the Completion Date shall be borne by the Seller and such part of the relevant charges and outgoings as is attributable to the period commencing on the day immediately following the Completion Date shall be borne by the Purchaser.

6.2 Apportionment of periodical receipts

All periodical receipts relating to the Assets including but not limited to:

(a) all periodical amounts, [***], received or receivable under any of the Business Contracts but excluding, for the avoidance of doubt, any upfront or milestone payments; and

(b) all rents and licence fees relating to or receivable in respect of the Assets,

shall be apportioned on a time basis so that such part of the relevant income and receipts as is attributable to the period ended on the Completion Date shall belong to the Seller and such part of the relevant payments and receipts as is attributable to the period commencing on the day immediately following the Completion Date shall belong to the Purchaser provided that any receipt or payment in respect of VAT shall belong to the party treated as making the supply for VAT purposes to which the receipt or payment relates.

6.3 Agreement of apportionments

As soon as reasonably practicable after the Completion Date, the Seller shall draw up and submit to the Purchaser a statement of: (i) the apportionments referred to in clauses 6.1 and 6.2; and (ii) the balance owing by one party to the other in respect of the same. The Purchaser shall have [***] from receipt of such statement to either (i) notify the Seller of its agreement with such statement; or (ii) send to the Seller a revised statement (and if the Purchaser does not send to the Seller such revised statement within [***], the Purchaser shall be taken to have agreed to the statement submitted to it by the Seller). The Seller and the Purchaser shall use their respective reasonable endeavours to agree any revised statement as far as possible. If, within [***] of receipt, the Seller has not agreed to all or part of the revised statement submitted to it by the Purchaser, either party may refer the disputed amount for determination in accordance with the procedure detailed in clause 13.2. Payment of the balance agreed, or determined pursuant to clause 13.2 (including partial payment of amounts relating to undisputed portions of the relevant statement), shall be made within [***] after such agreement or determination.

7. RESPONSIBILITY FOR LIABILITIES

7.1 The Purchaser shall be responsible for, shall pay, perform and discharge and shall indemnify the Seller Protected Parties against all debts, liabilities and obligations of the Seller under the Business Contracts, to the extent such obligations are (i) required to be paid or performed after the Completion Date or (ii) accrue and relate to ownership of the Assets in the period starting on the Completion Date (other than the Retained Liabilities) and following thereafter and all Losses suffered by the Seller Protected Parties as a result of the failure of the Purchaser to perform such debts, liabilities and obligations (the "**Assumed Liabilities**"). In addition, the Purchaser shall be responsible for, shall pay, perform and discharge and shall indemnify the Seller Protected Parties against all debts, liabilities and other obligations of the Purchaser and its Affiliates which relate to the ownership of the Assets in the period on and after the Completion Date and all Losses suffered by the Seller Protected Parties as a result of the failure of the Purchaser to perform such debts, liabilities and obligations after the Completion Date.

7.2 The Seller shall be responsible for and shall indemnify the Purchaser Protected Parties against all debts, liabilities and obligations of the Seller and its Affiliates which relate to or arise from the ownership of the Assets in the period up to and including the Completion Date (other than the Assumed Liabilities) ("**Retained Liabilities**") and all Losses suffered by the Purchaser Protected Parties as a result of the failure of the Seller or its Affiliates to perform such debts, liabilities and obligations.

7.3 The Purchaser will pay, satisfy, discharge and fulfil all claims and demands ("**Purchaser Demands**") relating to any Assumed Liability. If the Seller becomes aware that the Purchaser has failed to discharge any such Purchaser Demand, it may give notice of that fact to the Purchaser and the Purchaser shall provide reasonable evidence within [***] that the Purchaser Demand has been settled.

7.4 The Seller will pay, satisfy, discharge and fulfil all claims and demands ("**Seller Demands**") relating to any Retained Liability. If the Purchaser becomes aware that the Seller has failed to discharge any such Seller Demand, it may give notice of that fact to the Seller and the Seller shall provide reasonable evidence within [***] that the Seller Demand in question has been settled.

8. ACCOUNTS RECEIVABLE

The Seller shall remain responsible for collecting all Seller Accounts Receivable on its own behalf or on behalf of its Affiliates. If after the Completion Date the Purchaser or any of its Affiliates receives a sum in respect of a Seller Accounts Receivable or part thereof, the Purchaser shall hold it, or such part, on trust for the Seller and shall, within [***], pay it to the Seller. If the Seller or any of its Affiliates receives a sum in respect of a Purchaser Accounts Receivable or part thereof incurred in connection with sales of Strimvelis by the Purchaser or its Affiliates after the Completion Date, the Seller shall hold it, or such part, on trust for the Purchaser and shall, within [***], pay it to the Purchaser.

9. BUSINESS CONTRACTS

9.1 Assignment of Business Contracts

(a) In respect of those Business Contracts (other than the Consent Contracts), this Agreement shall constitute an assignment to the Purchaser of the benefit of and the assumption of the debts, liabilities and obligations (in accordance with clause 7.1) under all such Business Contracts with effect from the Completion Date.

(b) In respect of those Consent Contracts, this Agreement shall constitute an assignment of the benefit of and the assumption of the debts, liabilities and obligations (in accordance with clause 7.1) under any such Consent Contract with effect from the later of the Completion Date and any Consent being obtained or the novation of such Business Contract pursuant to clause 9.2.

9.2 Performance and enjoyment of Business Contracts until necessary consent obtained

From Completion until such time a Consent Contract is novated or such Consent is received in respect of such Consent Contract:

(a) the Seller shall use its Commercially Reasonable Efforts to procure that such Consent Contract is novated or such Consent is obtained, and the Purchaser shall co-operate with the Seller for such purpose (including the entering into of such assignment or novation on terms reasonably satisfactory to the parties as may be necessary);

(b) unless and until any such Consent Contract is novated or such Consent is obtained, the Seller shall from Completion hold such Consent Contract on trust for the Purchaser and its successors in title and the Purchaser shall from Completion (if such sub-contracting is permissible under the Consent Contract in question and the Purchaser is permitted by applicable law to do so), as the Seller's sub-contractor, perform all the obligations of the Seller under such Consent Contract and shall indemnify the Seller Protected Parties against any Losses relating to the performance of such Consent Contract after the Completion Date (other than Retained Liabilities) arising as a result of the Purchaser's performance under any such Consent Contract; and

(c) unless and until any such Consent Contract is novated or such Consent is obtained, the Seller shall (so far as it lawfully may do so and taking into account its obligations under this Agreement) give such assistance to the Purchaser which the Purchaser may reasonably require.

9.3 Repudiation of Business Contracts

No effect shall be given to clauses 9.2(b) and 9.2(c) if there is a material risk that the relevant Consent Contract would be treated as repudiated by the other party thereto or if the Seller would be in breach of its obligations under such Consent Contract to the other party thereto if effect were given thereto; provided that this clause 9.3 shall not relieve the Seller of its obligations under clause 9.2(a).

9.4 Termination of Business Contracts not assigned

At any time prior to the date on which a Consent is obtained for the assignment of a Consent Contract or such Consent Contract is novated, the Purchaser may elect by written notice to the Seller to withdraw its election to assume such Consent Contract and upon receipt of such election the Seller shall terminate such Consent Contract in accordance with clause 9.6.

9.5 No reduction in consideration for failure to obtain necessary consents

In the event that any Consent Contract is not novated or such Consent is not obtained, no reduction shall be made to the Consideration.

9.6 Cut-off date

In the event that any Consent Contract is not novated or such Consent is not obtained within six [***] after the Completion Date, then the provisions of clause 9.2(b) shall cease to apply then, at the election of the Seller, such Consent Contract shall cease to be a Consent Contract to be assigned to the Purchaser pursuant to this Agreement and the Seller shall be entitled, at the Seller's expense, to terminate such Consent Contract without any liability to the Purchaser therefor.

9.7 Payments

To the extent that any payment is made to the Seller after the Completion Date in respect of a Business Contract, which payment relates to the period following the Completion Date, the Seller shall receive the same as trustee and shall pay the amount of such payment to the Purchaser within [***] of receipt.

9.8 Telethon-HSR Agreement

Nothing in this Agreement shall amend, vary or relieve the Purchaser from any liability under the Telethon-HSR Agreement.

9.9 Unexecuted Contracts

As of the Completion Date the Unexecuted Contracts have been executed by the Seller or its Affiliate and sent to Telethon-HSR for signature but have yet to be executed by Telethon-HSR. The Parties agree that in the event Telethon-HSR executes any Unexecuted Contract within the period ending [***] following the Completion Date, such Unexecuted Contract shall become a Business Contract and shall be automatically assigned hereunder. If at the end of such [***] period any Unexecuted Contract remains unexecuted by Telethon-HSR the Seller shall be entitled to terminate such contract in accordance with clause 9.6. Further, the Seller agrees to promptly notify the Purchaser in writing upon becoming aware of the execution by Telethon-HSR of any Unexecuted Contracts.

10. EMPLOYEES

10.1 No Transfer

The parties acknowledge and agree that there are no employees of the Seller or any third party wholly or mainly assigned to the Assets. Accordingly, it is not envisaged that the Transfer Regulations will apply on or with effect from Completion so as to transfer the employment of any employees from the Seller or any third party to the Purchaser pursuant to the Transfer Regulations or otherwise with effect from Completion.

10.2 Undisclosed Employees

If any person employed or formerly employed by the Seller, any Affiliate of the Seller or any third party engaged by the Seller or any Affiliate (each a "**Seller Affiliate**") is found to have become, or alleges that he or she has become an employee of the Purchaser, any Purchaser Affiliate or any third party engaged by or on behalf of the Purchaser or any Affiliate of the Purchaser on or after Completion as a result of the operation of the Transfer Regulations or otherwise (an "**Undisclosed Employee**"), then:

(a) the Purchaser will upon becoming aware of any Undisclosed Employee and no later than [***] from Completion, notify the Seller in writing and a Seller Affiliate may, within [***] of Purchaser's written notification ("**Opportunity Period**"), offer employment to the Undisclosed Employee to take effect on the termination of the Undisclosed Employee's employment with the Purchaser or Purchaser Affiliate (as applicable);

(b) if no Seller Affiliate makes an offer of employment to the Undisclosed Employee during the Opportunity Period or the Undisclosed Employee does not accept the offer of employment from the Seller Affiliate during the Opportunity Period, the Purchaser or any Purchaser Affiliate (as applicable) may lawfully and properly terminate the employment of the Undisclosed Employee within [***] of the expiry of the Opportunity Period. In effecting and prior to such dismissal the Purchaser or any Purchaser Affiliate (as applicable) shall consult with and take into account the lawful and reasonable directions of the Seller;

(c) where the Purchaser has given written notification and the Purchaser or any Purchaser Affiliate terminates the employment of the Undisclosed Employee, the Seller shall indemnify the Purchaser and hold the Purchaser harmless (for itself and lawfully on behalf of each Purchaser Affiliate) against all Losses incurred by the Purchaser or any Purchaser Affiliate arising out of the employment and such termination of any Undisclosed Employee (excluding any liabilities for discriminatory acts or omissions by the Purchaser or any Purchaser Affiliate); and

(d) if the Undisclosed Employee accepts the Seller Affiliate's offer of employment then the Seller Affiliate shall inform the Purchaser or Purchaser Affiliate (as applicable) within [***] after such acceptance and the Purchaser or Purchaser Affiliate (as applicable) shall immediately release him or her from his or her employment and shall waive any right to notice of termination.

11. INTELLECTUAL PROPERTY

11.1 Business Intellectual Property

At Completion, the entire beneficial ownership of the Seller and its Affiliates in the Business Intellectual Property shall transfer from the Seller to the Purchaser (or such of the Purchaser's Affiliates as it shall designate), subject only to such filings and recordings as shall be necessary for the Purchaser (or such of the Purchaser's Affiliates as it shall designate) to become the legal, recorded or registered holder of such Business Intellectual Property. The Seller and the Purchaser have executed and delivered the Trade Mark and Domain Name Assignment to effect such

transfer. The Purchaser shall, at its own expense, file the Trade Mark and Domain Name Assignment and make such other required filings in respect of the Business Intellectual Property with the competent registrars, as it may deem necessary. The Purchaser shall bear the costs of registration and any transfer taxes or stamp duties resulting from the assignment and transfer of the Business Intellectual Property.

11.2 Licence Grants

The Seller hereby grants to the Purchaser, with effect from the Completion Date:

(a) an exclusive, worldwide, sub-licensable licence to the Patient-Level Clinical Data;

(b) an exclusive, worldwide, sub-licensable, licence to the Licensed Know-How in the Field for use in connection with the Programmes; and

(c) a non-exclusive, worldwide, sub-licensable licence to the Know-How constituting Other Seller IP in the Field for use in connection with the Programmes..

The Purchaser undertakes to use or sub-licence the Licensed Know-How or the Other Seller IP solely in connection with the Programmes.

11.3 Forum Meetings

(a) The Purchaser and the Seller shall meet at least [***] at times and places as agreed by the Alliance Managers (as defined in clause 17.1) of each party to discuss scientific progress of the Programmes, technical innovations and regulatory insights developed by the Purchaser and resulting from both the Programmes and the Purchaser's Programmes that could be of relevance to the Seller and its Affiliates' ongoing projects in ex vivo gene therapy (e.g., [***]) ("**Forum Meetings**"). [***]. The Purchaser shall require the attendance at each Forum Meeting of relevant senior managers with an understanding of the Programmes relevant to the agenda of such Forum Meeting. The Seller shall require the attendance at each Forum Meeting of any relevant senior employees which the Seller in its sole discretion considers necessary for the good conduct of such meeting.

(b) No later than [***] prior to any Forum Meeting the Purchaser shall (if applicable) provide to the Seller a written report summarising any technical innovations and regulatory insights which the Purchaser (acting reasonably) considers to be material ("**Disclosure Information**") and which it proposes should to be discussed at the next Forum Meeting in accordance with clause 11.3(b) (the "**Disclosure Report**"). Each Disclosure Report and any information of either party shared during the Forum Meeting shall be considered the Confidential Information of the party making the disclosure. The Disclosure Report shall include sufficient detail to allow the Seller to determine whether the Disclosure Information should be included in the agenda for discussion at the next Forum Meeting. The Seller will notify the Purchaser within [***] of receipt of the Disclosure Report whether any Disclosure Information should be removed from the agenda for the next Forum Meeting and not shared with the Seller (or alternatively shared under an agreed firewall procedure with a single individual(s) employee of the Seller or its Affiliate).

(c) The Alliance Managers shall keep accurate and complete confidential minutes of the Forum Meetings. Responsibility for taking such minutes shall alternate between the Parties and draft minutes shall be distributed to the non-drafting Alliance Manager for their review and comments within [***] after the date of each meeting. Any comments on the draft minutes must be provided to the relevant drafting party within [***] after receipt thereof. The Alliance Managers shall in good faith attempt to resolve any disputes as to the content of the minutes as quickly and reasonably as possible so as to have the final agreed-upon version quickly. If, however, the parties cannot agree on the content of the Alliance Manager meeting minutes, it shall be noted that the parties did not agree on the content of the minutes with respect to a specific item and each party's view shall be noted.

11.4 Arising IP

(a) In the event that the Purchaser generates any Arising Programme IP then the Purchaser shall:

(i) [***]; or

(ii) [***].

The Purchaser shall use reasonable efforts and act in good faith to present to the Seller such Arising Programme IP. The Purchaser will grant and hereby grants to the Seller and its Affiliates a worldwide, irrevocable, non-exclusive, paid-up, royalty-free, sublicensable (solely as permitted by this paragraph) licence to the Arising Programme IP for use in connection with a GSK Programme outside the Field provided that the Seller or its Affiliate shall only be entitled to sublicense any Arising Programme IP in connection with a GSK Programme outside the Field. Any such licence granted by the Seller or its Affiliate shall include appropriate provisions with respect to the licensee's duty of confidentiality. The Seller's rights under the licence which has been granted pursuant to this clause 11.4 shall be subject to clause 14;

(b) In the event that the Purchaser generates any Purchaser Platform IP, [***]:

(i) [***]; or

(ii) [***].

[***].

11.5 Licence-Back

(a) The Purchaser hereby grants to the Seller, with effect from the Completion Date, a non-exclusive, perpetual, worldwide, sublicenseable (subject to clause 11.5(b)) paid-up, right and licence solely for any purpose outside the Field to use:

(i) any Know-How related to the Product Registrations, the items referred to in paragraphs (2) and (3) of Exhibit 2 (Commercial Information) or Regulatory Information; and

(ii) to the extent that it is permitted to do so, any Know-How in existence as at the Completion Date licensed to the Purchaser as a result of the assignment of the MolMed Agreement, the Telethon-HSR Agreement and the [***] for the Seller to continue to benefit from the licences granted pursuant to clauses 3.2-3.3 (inclusive) of the MolMed Agreement, the Telethon-HSR Agreement, and clauses 2.1-2.3 (inclusive) of the [***];

in each case excluding any Patient-Level Clinical Data.

The Seller's rights under the licence granted pursuant to this clause 11.5 shall be subject always to the Seller's compliance with the terms of clause 14. For the avoidance of doubt, the Seller has retained the right to use the Licensed Know-How outside the Field.

(b) The Seller and its Affiliates shall have no right to grant a sublicence to any Intellectual Property included in the licence granted to the Seller or its Affiliate pursuant to clause 11.5(a) other than in connection with a GSK Programme outside the Field. Any such licence granted by the Seller or its Affiliate shall include appropriate provisions with respect to the licensee's duty of confidentiality.

11.6 Unblocking-Licence

The Seller hereby grants to the Purchaser, with effect from the Completion Date, a non-exclusive, perpetual, worldwide, sublicenseable, paid-up, right and license to use any Intellectual Property of the Seller protected by a Valid Claim in existence at the Completion Date, which is necessary for the development and commercialisation of (i) Therapeutic Products that were in clinical development pursuant to the Programmes prior to the Completion Date and (ii) Strimvelis. [***]

11.7 Retained Information and Rights

The Seller shall be entitled to retain copies of or, to the extent the Seller is required by applicable law to keep the originals, the originals of, all Regulatory Information, Clinical Data, Commercial Information, and Production Information and the Licensed Know-How for use solely:

(a) for the Seller's internal record keeping purposes;

(b) for reference as required for purposes internal to the Seller and to comply with applicable laws and regulations; and/or

(c) to the extent required for the Seller to exercise its rights pursuant to clause 11.5;

provided that the Seller shall at all times keep such copies and originals confidential in accordance with clause 16 as if such information were the Confidential Information of the Purchaser and such rights shall be subject to the provisions of clause 14.

12. PRIORITY REVIEW VOUCHERS

12.1 The Purchaser and its Affiliates shall use their Commercially Reasonable Efforts to obtain Sale PRVs including but not limited to submitting a voucher request in the submission of the applicable biological licensing application.

12.2 The parties agree that the first Sale PRV (if any) legally granted to the Purchaser or its Affiliates shall beneficially belong to the Seller with effect from the Completion Date. The Purchaser shall transfer legal ownership to the first such Sale PRV that it receives to the Seller. The Purchaser shall, at least once every [***], and in any event on reasonable request of the Seller, inform the Seller of the status of any such Sale PRV process. For the avoidance of doubt, other than the first such Sale PRV which shall be subject to the terms of this clause 12.1, the Purchaser or its Affiliates shall retain full ownership of any other PRV(s) obtained at any time, subject to the Seller's right of acquisition set out in clause 12.3.

12.3 Following receipt and transfer of the first Sale PRV to the Seller, the Purchaser shall inform the Seller promptly of receipt of any subsequent Sale PRV granted to the Purchaser or its Affiliate relating to a Royalty Product, and the Seller shall following receipt of such notification have the exclusive right to acquire such Sale PRV for [***]. The Seller shall, within [***] of receipt of notice from the Purchaser, either (i) confirm it wishes to acquire the Sale PRV, or (ii) confirm that it does not wish to acquire the Sale PRV provided that if no notice has been received by the Purchaser from the Seller by the end of such [***] period, the Seller shall be considered to have confirmed that it does not wish to acquire the Sale PRV.

12.4 In the event that the Seller wishes to acquire the Sale PRV, it shall do so within [***] of the date of the notice given by the Seller pursuant to clause 12.3. [***]

12.5 If the Seller does not wish to acquire the Sale PRV and in the event of any subsequent sale of the Sale PRV by the Purchaser or its Affiliate to a third party for a price equal to or in excess of [***] and the Purchaser shall within [***] of receipt of such amounts pay to the Seller an amount equal to [***] of any amount actually received by the Purchaser or its Affiliate in excess of [***].

12.6 For the avoidance of doubt if the Seller does not wish to acquire the Sale PRV (as described in clause 12.3 above) the Purchaser shall not be obliged to sell the Sale PRV but may, at its discretion, retain the Sale PRV for its own use.

13. RECORDS, AUDIT AND AUDIT DISAGREEMENT

13.1 Records and Audit

(a) Both parties shall ensure that its Affiliates, sub-licensees, distributors, and any other persons (together, the "**Audited Entities**") shall keep or cause to be kept complete and accurate records which are relevant to any payment to be made after Completion under this Agreement, including without limitation, records on Net Sales and calculations of royalty payments, milestone payments and Royalty Reports.

(b) At the request and expense of the Seller, after Completion the Audited Entities shall, upon [***] prior written notice, permit the Seller, its authorised representatives and/or an independent certified public accountant appointed by the Seller, at reasonable times and upon reasonable notice, to examine such records as may be necessary to determine, with respect to any calendar year ending not more than [***] prior to the Seller's request, the correctness or completeness of any report or payment made under this Agreement provided that the Seller may not exercise its rights pursuant to this clause 13.1(a) more than [***].

(c) The Seller shall bear the expenses of such independent certified public accountant related to the performance of any such audit, unless such audit discloses a deviation to the detriment of the Seller of more than [***] from the amount of the original report, or payment calculation. In such case, the Purchaser shall bear the full cost of the performance of such audit.

(d) If such audit reveals that the Audited Entity has failed to accurately report information, and the result was underpayment, the Purchaser shall promptly pay any amounts due to the Seller together with interest on such amount, calculated from the date accruable at the Default Rate. In the event of overpayment, the Seller shall promptly pay any amounts due to the Purchaser together with interest on such amount, calculated from the date accruable at the Default Rate.

13.2 Audit Disagreement

(a) If there is a dispute between the parties related to any audit performed pursuant to clause 13.1 or any financial information to be provided under any provision of this Agreement, either party may refer the issue (an "**Audit Disagreement**") to an independent certified public accountant for resolution. In the event an Audit Disagreement is submitted for resolution by either party, the parties shall comply with the following procedures:

(i) the party submitting the Audit Disagreement for resolution shall provide written notice to the other party that it is invoking the procedures of this clause 13.2;

(ii) within [***] of the giving such notice, the parties shall jointly select a recognised international accounting firm to act as an independent expert to resolve such Audit Disagreement;

(iii) the Audit Disagreement submitted for resolution shall be described by the parties to the independent expert, which description may be in written or oral form, within [***] of the selection of such independent expert;

(iv) the independent expert shall render a decision on the matter as soon as practicable and no later than [***] from the date of referral to the expert;

(v) the decision of the independent expert shall be final and binding unless such Audit Disagreement involves alleged fraud, breach of this Agreement or construction or interpretation of any of the terms and conditions hereof.

(b) All fees and expenses of the independent expert, including any third party support staff or other costs incurred with respect to carrying out the procedures specified at the direction of the independent expert in connection with such Audit Disagreement, shall be borne by the party against whom such expert rules.

14. RESTRICTIVE COVENANTS

14.1 In consideration of the payment of the Consideration, the Seller undertakes to the Purchaser that, except with the consent in writing of the Purchaser, it will not (and will procure that none of its Affiliates or any third party acting on behalf of the Seller or its Affiliates will), carry on any activities in the Field, nor licence any person the Licensed Know-How to carry on activities in the Field, for a period of [***] following Completion.

14.2 The Seller acknowledges on its own behalf and on behalf of each of its Affiliates that it considers the restrictions contained in this clause 14, each of which shall be construed as a separate undertaking, are reasonable in the interests of both the Seller and the Purchaser and are necessary for the protection of the goodwill and Confidential Information relating to the Programmes. Each of the undertakings contained in clause 14.1 is a separate undertaking by the Seller in relation to its interests and shall be enforceable by the Purchaser separately and independently of their rights to enforce any one or more of the other covenants contained in clause 14.1. If any such undertaking shall be found to be void or voidable but would be valid and enforceable if some part or parts of it were deleted, then such undertaking shall apply with such modifications as may be necessary to make it valid and enforceable.

14.3 The Purchaser confirms that, as at the Completion Date, it does not currently have, and does not currently intend to initiate, any programme to develop a product which would compete with any of the Royalty Products (excluding OTL-101).

15. WARRANTIES

15.1 Warranties of the Seller

(a) The Seller warrants to the Purchaser that the Warranties contained in Schedule 5 are true and accurate as at the Completion Date, subject to any matter fairly disclosed in the Data Room or the Disclosure Letter, in each case with sufficient detail to identify the nature and scope of the matter disclosed. For the avoidance of doubt, any information included in the PowerPoint slide deck dated [***] prepared by the Purchaser for presentation to the Purchaser's board in connection with the transaction set forth herein shall be deemed to have been fairly disclosed to the Purchaser.

(b) The Purchaser shall not be entitled to make a Warranty Claim to the extent that a Purchaser Knowledge Party has at the Completion Date actual (but not imputed or constructive) knowledge of the relevant facts or circumstances which may give rise to a Warranty Claim (for this purpose, the "**Purchaser Knowledge Parties**" shall mean any of the following persons: [***], [***], [***], [***], [***], [***], [***], [***] and [***]).

15.2 Separate and independent warranty

Each of the Warranties shall be construed as a separate and independent warranty and (except where this Agreement provides otherwise) shall not be limited or restricted in its scope by reference to, or inference from, any other term of another Warranty or any term of this Agreement (subject always to the Purchaser not being able to recover more than once in respect of the same loss).

15.3 Knowledge, information and belief and disclosure

Where a warranty is qualified by the expression "to the knowledge of the Seller" or "so far as the Seller is aware" or by a similar expression, such expression shall be deemed to mean the actual knowledge of a Seller Knowledge Party (for this purpose, "**Seller Knowledge Party**" means any of the following persons: [***], [***], [***], [***], [***], [***], [***], [***], [***], [***], [***] and [***].)

15.4 Limitations

The Purchaser acknowledges and agrees that:

(a) notwithstanding anything to the contrary set out in this Agreement, no other statement, promise or forecast made by or on behalf of the Seller may form the basis of, or be pleaded in connection with, any Claim and, the Purchaser acknowledges and agrees that the Seller makes no representation or warranty as to (a) any projections, forecasts, estimates or budgets delivered to or made available to the Purchaser of future revenues, future results of operations (or any component thereof), future cash flows or future financial condition (or any component thereof) of the Assets and the Programmes or their future business and operations or otherwise; or (b) any other information or documents made available to the Purchaser with respect to the Assets and the Programmes;

(b) it is an informed and sophisticated person, and has engaged expert advisers experienced in the evaluation and acquisition of assets such as the Assets. The Purchaser has conducted due diligence in relation to the Assets and the Programmes and has been provided with, and has evaluated, such documents and information as it has deemed necessary to enable it to make an informed and rational decision with respect to the execution, delivery and performance of this Agreement;

(c) at the time of entering into this Agreement it is not actually aware of any breach by the Seller of any Warranty; and

(d) the Seller's liability in respect of Warranty Claims is further limited by the provisions of Schedule 6.

15.5 Warranties of the Purchaser

The Purchaser warrants to the Seller as at the Completion Date that:

(a) the Purchaser and each Affiliate of the Purchaser which is a party to any Transaction Document ("**Purchaser Relevant Affiliate**") is a corporation, limited liability company or other legal entity duly organized, validly existing and in good standing under the laws of the jurisdiction of its or their incorporation;

(b) the Purchaser and each Purchaser Relevant Affiliate has obtained all corporate authorisations required to empower it to enter into and to perform its obligations under the Transaction Documents and the execution, delivery and performance by the Purchaser and each Purchaser Relevant Affiliate of the Transaction Documents and the consummation of the transactions contemplated by the Transaction Documents are within the power and authority of the Purchaser and/or the Purchaser Relevant Affiliates (as applicable);

(c) neither the execution, delivery and performance of any Transaction Document nor the consummation of the transactions contemplated by the Transaction Documents by the Purchaser or any Purchaser Relevant Affiliate will:

(i) breach, violate, result in default under, or conflict with the provisions of the constitutional documents of the Purchaser or any Purchaser Relevant Affiliate;

(ii) contravene or conflict with, or amount to a violation or breach of, any applicable laws or regulations in any relevant jurisdiction to which the Purchaser or any Purchaser Relevant Affiliate is subject; or

(iii) amount to a violation or default with respect to any relevant order, decree or judgment of any Regulatory Authority or other Governmental Entity in any jurisdiction to which the Purchaser or any Purchaser Relevant Affiliate is a party or by which the Purchaser or any Purchaser Relevant Affiliate is bound; or

(iv) result in a breach of or constitute a default under any instrument to which the Purchaser or any Purchaser Relevant Affiliate is a party or by which the Purchaser or any Purchaser Relevant Affiliate is bound;

(d) the Transaction Documents have been duly executed and delivered by the Purchaser and each Purchaser Relevant Affiliate that is a party thereto (as the case may be) and constitute valid and legally binding obligations of the Purchaser and/or the Purchaser Relevant Affiliate that is a party thereto in accordance with their respective terms, except as may be limited by applicable bankruptcy, insolvency, moratorium or other similar laws in effect relating to or affecting creditors' rights generally;

(e) no action (including any authorisation, clearance, consent or approval) by or in respect of, or filing with, any Regulatory Authority or other Governmental Entity or any third party is required by the Purchaser or any Purchaser Relevant Affiliate for, or in connection with, the valid and lawful authorisation, execution, delivery and performance by the Purchaser or any Purchaser Relevant Affiliate of the Transaction Documents or the consummation of the transactions contemplated thereby;

(f) no order has been made and no resolution has been passed for the winding up of the Purchaser or any Affiliate of the Purchaser or for a provisional liquidator or manager to be appointed in respect of the Purchaser or any Affiliate of the Purchaser, no meeting has been convened and, so far as the Purchaser is aware, no petition has been presented for the purposes of the winding up of the Purchaser or any Affiliate of the Purchaser and no other process whereby the business of the Purchaser or any Affiliate of the Purchaser is terminated and the assets of the Purchaser or any relevant Affiliate are distributed amongst its creditors and/or shareholders or any other proceedings under any applicable insolvency, reorganisation or similar laws in any relevant jurisdiction have taken place, and no events or circumstances analogous to any of the above referred to in this paragraph have occurred in or outside England; and

(g) the Purchaser acknowledges receipt of the 'Prevention of Corruption'-Third Party Guidelines and confirms it shall perform its obligations under this Agreement in all material respects in accordance with the principles set out therein.

15.6 No Claim against employees etc

The Purchaser acknowledges and agrees that it has no rights or claim against any director, officer, employee, agent or professional adviser of the Seller or any Affiliate of a Seller (including any person on which or whom it may have relied before agreeing to the terms of this Agreement, the Disclosure Letter or any Transaction Document) and to the extent that any such rights or claim exist, the Purchaser irrevocably and unconditionally waives such claim and releases any director, officer, employee, agent or professional adviser of the Seller and any Affiliate of a Seller from any liability whatsoever in respect of such claim.

16. ANNOUNCEMENTS, CONFIDENTIALITY AND RETURN OF INFORMATION

16.1 Prior approval of announcements

(a) The parties agree that the public announcements of the execution of this Agreement shall be substantially in the form of the press releases attached as Part 1 of Schedule 7 and that the final version shall be agreed in writing in advance by each party.

(b) In addition, the parties recognise that each party may from time to time desire to issue additional press releases and make other public statements or disclosures regarding the subject matter of this Agreement, and hereby agree that such disclosures shall be permitted without the other party's consent, to the extent that such additional releases (i) update the press releases attached as Schedule 7 or any subsequent press release published in accordance with this clause 16.1; (ii) are based on public information.

(c) Any other press release or announcement released publicly and in writing ("**Release**") relating to this Agreement or to the performance hereunder shall be subject to the following:

(i) until [***], the prior written consent of the Purchaser and the Seller shall be required within [***] of receipt of such Release (in each case, such consent not to be unreasonably withheld or delayed). To the extent required, each party shall promptly (and in any event not later than [***] after receipt of a Release) provide any drafting comments to the other party in respect of such Release;

(ii) from [***], the consent of the Seller (such consent not to be unreasonably withheld or delayed) shall be required within [***] of receipt of such Release only if the Seller is referred to in the Release subject to the exemptions set out in paragraph 16.1(b) provided always that this clause 16.1(c)(ii) shall not apply if the only reference to the Seller is the acknowledgement required by clause 16.1(c)(iii)(A) below. To the extent required, each party shall promptly (and in any event not later than [***] after receipt of a Release) provide any drafting comments to the other party in respect of such Release;

(iii) from [***], the consent of the Purchaser (such consent not to be unreasonably withheld or delayed) shall be required within [***] of receipt of such Release only if the Purchaser or the Programmes are referred to in the Release, subject to the exemptions set out in paragraph 16.1(b) provided that this clause 16.1(c)(iii) shall not apply if the only reference to the Purchaser is the acknowledgment required by 16.1(c)(B). To the extent required, each party shall promptly (and in any event not later than [***] after receipt of a Release) provide any drafting comments to the other party in respect of such Release,

provided, however, that from the Completion Date and continuing past [***]:

(A) any Release by the Purchaser will contain a statement substantially in the form as set out in Schedule 7, Part 2 which acknowledges the Seller's and Telethon-HSR's contributions to the Programmes;

(B) any Release by the Seller will contain a statement substantially in the form as set out in Schedule 7, Part 2 which acknowledge the Purchaser's acquisition and continued development and commercialisation of the Programmes and a Royalty Products; and

(C) any disclosure which is required by law or regulation or by applicable stock exchange rules, as reasonably advised by the disclosing party's counsel, may be made without the prior consent of the other party, although the Seller or, as the case may be, the Purchaser shall be given prompt notice of any such required disclosure. The parties acknowledge that, for the purpose of giving guidance to investors under applicable stock exchange rules, general information regarding this Agreement may be disclosed including upfront payments and cumulative total contingent success payments.

16.2 Confidentiality

(a) Subject to clause 11, each party shall treat as strictly confidential and will not disclose any Confidential Information of the other party. Each party agrees that Confidential Information will include without limitation:

(i) the provisions of this Agreement or any document or agreement entered into pursuant to this Agreement; or

(ii) the negotiations leading up to or relating to this Agreement.

(b) The Seller shall treat as strictly confidential and not disclose any Core IP in a manner that directly refers to the Purchaser or the Programmes or which would by its nature enable any of the Programmes or the Purchaser to be directly identified.

(c) The restrictions in clause 16.2(a) and (b) shall not apply to any disclosure of information by a party if and to the extent the disclosure is:

(i) required by the law of any jurisdiction;

(ii) required by any applicable securities exchange, supervisory, regulatory or Governmental Entity to which the relevant party is subject or submits, wherever situated, whether or not the requirement for disclosure has the force of law;

(iii) made to the relevant party's professional advisers, auditors or bankers or the professional advisers, auditors or bankers of any other member of the relevant party's group of companies;

(iv) of information that has already come into the public domain through no fault of the relevant party or any other member of that party's group of companies; or

(v) required or permitted by the terms of this Agreement.

17. JOINT TRANSITION COMMITTEE

17.1 As soon as reasonably practical following the Completion Date, the parties will establish a joint steering committee (the "**Joint Transition Committee**" or "**JTC**"), comprised of two core representatives (one appointed by the Seller and one appointed by the Purchaser) and two individuals (one appointed by the Seller and one appointed by the Purchaser) responsible for managing the interactions between the Parties ("**Alliance Managers**"). Each party shall collectively have one (1) vote on the JTC. Each party shall provide the other party with written notice of its initial representatives on the JTC within ten (10) Business Days of the Completion Date. The parties may change the total number of core seats on the JTC by mutual agreement, provided that each party shall always hold the same number of seats on the JTC as the other party. Each party may substitute or replace any of its representatives on the JTC at any time for any reason upon written notice to the other party.

17.2 From the Completion Date and until the later of (a) expiry of the last Service Term as set out in the TSA or (b) the conclusion of the Programme Transfer Plan as set out in Schedule 10 (the "**JTC Conclusion Date**"), the JTC shall meet on at least a [***] basis (and on a more frequent basis as may be agreed by the JTC), which may be telephonically, by video conference, or in person. From the JTC Conclusion Date, the Alliance Managers shall (i) serve as the primary points of contract for matters under this Agreement and (ii) meet every [***] until the [***] anniversary of the Completion Date to discuss all matters relating to the obligations of the Parties under this Agreement including, but not limited to, the Programmes, the services to be provided under the Transition Services Agreement, the Programme Transfer Plan, communications, and the scheduling and management of Forum Meetings.

17.3 The members of the JTC and the Alliance Managers also may be convened, polled or consulted from time to time by means of telecommunications, video conferences, electronic mail or correspondence, as deemed necessary or appropriate. The venue for the face-to-face meetings shall alternate between the offices of the Seller in the UK (including central London, Brentford or Stevenage) and the offices of the Purchaser in the UK. The agenda items for each meeting shall be identified a week in advance of such meeting, and the parties shall identify suitable attendees for such meeting. Each party shall be responsible for its own expenses including travel and accommodation costs to attend such JTC or Alliance Manager meetings. The JTC and the Alliance Managers, as applicable, shall keep accurate and complete confidential minutes of its meetings. Responsibility for taking such minutes shall alternate between the Parties and draft minutes shall be distributed to the other JTC members or the Alliance Managers for their review and comments within [***] after the date of each meeting. Any comments on the draft minutes must be provided to the relevant drafting party within [***] after receipt thereof. The JTC members or the Alliance Managers shall in good faith attempt to resolve any disputes as to the content of the JTC minutes as quickly and reasonably as possible so as to have the final agreed-upon version quickly. If, however, the parties cannot agree on the content of the JTC or Alliance Manager meeting minutes, it shall be noted that the parties did not agree on the content of the minutes with respect to a specific item and each party's view shall be noted.

17.4 The JTC and Alliance Managers shall be responsible for the following:

(a) directing the implementation of the Programme Transfer Plan and the services to be provided under the Transition Services Agreement, and facilitating the transfer of information between the parties for the execution of the Programme Transfer Plan and the Transition Services Agreement;

(b) regularly reviewing the activities, progress and results of the Programme Transfer Plan and Transition Services Agreement to ensure, to the extent reasonably practical, that the parties are meeting their respective commitments; and

(c) performing such other duties as are specifically agreed to in writing by the parties or which are expressly set out in a Transaction Document;

provided, however, the JTC and the Alliance Managers shall not have the power to amend or modify, or waive compliance with, this Agreement or any Transaction Document, and no decision of the JTC or Alliance Managers exercising a deciding vote as provided in this clause 17, shall be in contravention of the provisions of any Transaction Document or shall result in any obligations being imposed on a party (including without limitation any increase in costs or resources), without the express prior written consent of such party following their internal governance approval processes for such changes to the Transaction Documents and the agreements set out therein.

17.5 From the Completion Date and until the conclusion of the last Forum Meeting as described in clause 11.3 continue, the Alliance Managers shall be responsible for the following:

(a) Providing and receiving the Disclosure Information and Disclosure Reports as set forth in clause 11.3(b);

(b) Organizing and conducting the Forum Meetings as set out in clause 11.3(a);

(c) Serving as the primary point of contact for each party for the exchange of proposed communications to be disclosed under clause 16.1;

(d) Following the JTC Conclusion Date, to serve as the primary initial point of contact between the Parties for any matter included in the Transaction Documents.

17.6 All decisions of the JTC shall be made by unanimous consent at a meeting where the quorum is met. A quorum for a meeting shall require at least (i) one Seller member and (ii) one Purchaser member. No meeting shall proceed without the quorum for a meeting being present and all decisions passed at a meeting where the abovementioned quorum is not present shall not be valid unless mutually agreed in writing by the quorum of JTC members from each party. The JTC shall use its reasonable efforts to reach consensus on all matters presented to the JTC for decision. If, however, the JTC is unable to reach a consensus on a matter before the JTC then the matter shall be escalated to Senior Managers. The Senior Managers shall meet within [***] of escalation of the matter to them to discuss and attempt to resolve the issue, acting reasonably and in good faith. If, however, after good faith attempts to reach agreement to resolve such issue, the Senior Managers are unable to reach agreement within [***] of their initial meeting to discuss the issue (or if the Senior Managers fail to meet for whatever reason, within [***] of the referral to the Senior Managers), then either party may submit such matter to dispute resolution in accordance with clause 31 other than where such matter concerns [***], in which case the Seller Senior Manager shall have the final decision-making authority.

18. VAT, SET-OFF AND WITHHOLDING TAX

18.1 All payments or other consideration given under this Agreement are each exclusive of any VAT.

18.2 Any VAT chargeable in respect of the Initial Consideration shall be paid by the Purchaser at the same time as payment of the Initial Payment, subject to the production of a valid VAT invoice prior to payment. For the avoidance of doubt the Parties agree that the value of the Consideration Shares for the purposes of this Agreement (including for VAT purposes) is £4.019 per share.

18.3 Any VAT chargeable in respect of any royalty or milestone payment payable by the Purchaser under the provisions of clause5.3 of this Agreement shall be payable by Purchaser in accordance with the provisions of clause 5.3(j).

18.4 Where VAT is chargeable in respect of any supply made by the Purchaser under this Agreement, the Seller shall pay any such VAT promptly following receipt of a valid VAT invoice from the Purchaser.

18.5 If any VAT originally paid by the recipient of the relevant supply for VAT purposes to the supplier in accordance with the terms of this Agreement is in whole or in part subsequently determined not to have been properly chargeable, the supplier shall pay an amount equal to any such VAT paid to the recipient within [***] of such determination. The supplier of the relevant supply in respect of which VAT is determined not to have been chargeable shall promptly notify the recipient in writing following it determining or otherwise becoming aware of HM Revenue & Customs determining that such VAT is not chargeable (in whole or in part). The recipient shall notify the supplier in writing if it first becomes aware that any VAT it has paid is determined not to be properly chargeable (in which case, the date of such notification shall be deemed to be the date of determination).

18.6 All payments made under this Agreement by one party to another shall be made gross and free of any right of counterclaim or set-off and without deduction or withholding for or on account of any present or future Taxation unless in the event that one party (the payor) is required to withhold or deduct an amount equal to any Tax required by law to be deducted or withheld from the amount due to the recipient of the payment (the payee), the payor shall account for such Tax to the relevant Tax Authority within the time allowed by applicable law and secure and send to the payee the reasonable evidence of payment of such Tax. Any such Tax withheld or deducted shall be treated as having been paid by the payor to the payee for all purposes of this Agreement.

18.7 The Purchaser and the Seller will cooperate with respect to all documentation required by any Tax Authority or which may be reasonably requested by the other party to secure a reduction in the rate of applicable withholding taxes or to permit the other party to obtain a repayment of or credit for all withholding tax withheld or deducted in respect of any payment under this Agreement.

18.8 The Purchaser and the Seller respectively waive and relinquish any right of counterclaim or set-off against payments which (in the case of the Purchaser) the Purchaser is or may be liable to make to the Seller or (in the case of the Seller) the Seller is or may be liable to make to the Purchaser pursuant to this Agreement or otherwise.

19. WRONG POCKETS

19.1 Purchaser to transfer assets

For a period of [***] from the TSA Expiration Date, if the legal title to or the beneficial interest in any asset or property of the Seller or any of its Affiliates which does not constitute an Asset is transferred to or vested in the Purchaser or any Affiliate of the Purchaser at Completion, the Purchaser or relevant Affiliate of the Purchaser, as the case may be, shall be deemed to hold such asset or property (the "**Seller Required Asset(s)**") on trust and as bailee for the Seller or any Affiliate of the Seller, as the case may be, and the Purchaser or relevant Affiliate of the Purchaser shall, at the Seller's request and at the expense of the Seller, as soon as practicable and on terms that no consideration is provided by any person for such transfer:

(a) execute such deeds or documents as may be reasonably necessary for the purpose of transferring (free of any Encumbrance created by the Purchaser or any of its Affiliates after Completion) the relevant interest in such Seller Required Asset(s) to the Seller or any Affiliate of the Seller or as the Seller may direct; and

(b) do or procure to be done all such further reasonable acts or things and procure the execution of all such other documents as the Seller (for itself or any of its Affiliates) may reasonably request for the purpose of vesting the relevant interest in such Seller Required Asset(s) in the Seller or any Affiliate of the Seller, as the case may be.

19.2 Purchaser's obligations to notify

The Purchaser shall notify the Seller as soon as reasonably practicable upon it coming to its attention that there are any Seller Required Asset(s) in its possession or control or in the possession or control of any Affiliate of the Purchaser provided that the provisions of clause 19.1 shall only apply during the period of [***] from the TSA Expiration Date.

19.3 Seller to transfer assets

For a period of [***] from the TSA Expiration Date, if the legal title to or the beneficial interest in any asset or property of the Seller or any of its Affiliates which constitutes an Asset (or which is directly and specifically related to the Programmes) is not transferred to or vested in the Purchaser or any Affiliate of the Purchaser at Completion, the Seller or relevant Affiliate of the Seller, as the case may be, shall be deemed to hold such asset or property (the **"Purchaser Required Asset(s)"**) on trust and as bailee for the Purchaser or any Affiliate of the Purchaser, as the case may be, and the Seller or relevant Affiliate of the Seller shall, at the Purchaser's request and at the expense of the Seller, as soon as practicable and on terms that no consideration is provided by any person for such transfer:

(a) execute such deeds or documents as may be reasonably necessary for the purpose of transferring (free of any Encumbrance created by the Seller or any of its Affiliates after Completion) the relevant interest in such Purchaser Required Asset(s) to the Purchaser or any Affiliate of the Purchaser or as the Purchaser may direct; and

(b) do or procure to be done all such further reasonable acts or things and procure the execution of all such other documents as the Purchaser (for itself or any of its Affiliates) may reasonably request for the purpose of vesting the relevant interest in such Purchaser Required Asset(s) in the Purchaser or any Affiliate of the Purchaser, as the case may be.

19.4 Seller's obligations to notify

(a) The Seller shall notify the Purchaser as soon as reasonably practicable upon it coming to its attention that there are any Purchaser Required Asset(s) in its possession or control or in the possession or control of any Affiliate of the Seller provided that the provisions of clause 19.3 shall only apply during the period of [***] from the TSA Expiration Date.

(b) If, acting reasonably and in good faith, the Seller is unable to comply with its obligations under clause 19.3 as a result of there being no relevant employees with the appropriate skills employed by the Seller or its Affiliates at such time in order to appropriately advise the Seller in respect of the Purchaser Required Assets(s), then the issue shall be referred to the Senior Managers. The Senior Managers shall meet within [***] of escalation of the matter to them to discuss and attempt to resolve the issue, acting reasonably and in good faith. If after good faith attempts to reach agreement to resolve such issue, the Senior Managers are unable to reach agreement within [***] of their initial meeting to discuss the issue (or if the Senior Managers fail to meet for whatever reason, within [***] of the referral to the Senior Managers), then either party may submit such matter to dispute resolution as set out in clause 32.3(b).

19.5 Update of Exhibits for Know-How identified after the Completion Date

If following the Completion Date and ending on the date that is [***] from the TSA Expiration Date, the Seller identifies any Know-How that was generated by or on behalf of the Seller for use exclusively with the Programmes and that should have been included in Exhibit 1 (Clinical Trial Master File Information) or Exhibit 3 (Production Information) then the Seller shall notify the Purchaser and the Parties agree to update the relevant Exhibit.

20. MATERIAL BREACH; TERMINATION

Material CRE Breach

20.1 If at any time the Seller determines that the Purchaser is in material breach of its obligations to utilise its Best Endeavours or Commercially Reasonable Efforts (as the case may be) to perform its obligations set out in clauses 5.2 (b), (c) and (d) in respect of any Royalty Product ("**Material CRE Breach**"), the Seller may issue a notice in writing to the Purchaser setting out in reasonable detail the reasons and justifications for such determination (a "**Warning Notice**").

20.2 The parties shall, following the issue of a Warning Notice by the Seller, enter into good faith negotiations to reach mutual agreement as to the steps which should be taken to address the concerns detailed by the Seller.

20.3 If the parties reach an agreement under clause 20.2 within [***] of the date of the Warning Notice as to the steps which should be taken to address the concerns of the Seller detailed in the Warning Notice:

(a) the Purchaser shall, within [***] reaching agreement with the Seller (as described above) deliver to the Seller a plan for addressing the Seller's concerns detailed in the Warning Notice (a **"Remedial Action Plan"**);

(b) the Seller shall have [***] to approve the Remedial Action Plan ([***]), provided that such Remedial Action Plan will be deemed to have been approved by the Seller if no response is received from the Seller by the date [***] following receipt by the Seller of the Remedial Action Plan;

(c) if the Remedial Action Plan is not approved by the Seller, the provisions of clause 20.4 shall apply. If the Remedial Action Plan is approved by the Seller, the Purchaser shall commence implementation of the agreed Remedial Action Plan and the parties (acting reasonably) shall agree on an appropriate monitoring plan to review the progress of the Remedial Action Plan; and

(d) if at any time, in the reasonable opinion of the Seller, the Purchaser is not complying with the terms of the Remedial Action Plan, the issue shall be referred to the Senior Managers. The Senior Managers shall meet within [***] of escalation of the matter to them to discuss and attempt to resolve the issue, acting reasonably and in good faith. If after good faith attempts to reach agreement to resolve such issue, the Senior Managers are unable to reach agreement within [***] of their initial meeting to discuss the issue (or if the Senior Managers fail to meet for whatever reason, within [***] of the referral to the Senior Managers), then either party may submit such matter to dispute resolution as set out in clause 32.3(b).

20.4 If the parties cannot reach agreement: (a) under clause 20.1 within [***] of the date of the Warning Notice as to the steps which should be taken to address the concerns of the Seller detailed in the Warning Notice or (b) under clause 20.3(b) in respect of the Remedial Action Plan, the matter shall in the first instance be escalated to the Senior Managers**.** The Senior Managers shall meet within [***] of escalation of the matter to them to discuss and attempt to resolve the issue, acting reasonably and in good faith. If, however, after good faith attempts to reach agreement to resolve such issue, the Senior Managers are unable to reach agreement within [***] of their initial meeting to discuss the issue (or if the Senior Managers fail to meet for whatever reason, within [***] of the referral to the Senior Managers), then either party may submit such matter to dispute resolution as set out in clause 32.3(b).

20.5 Following compliance with the required actions set out above in clauses 20.1 to 20.4 (inclusive), if it is determined in accordance with clause 32.3 that there has been a Material CRE Breach by the Purchaser in respect of the relevant Royalty Product then the parties agree that the sole remedy for such Material CRE Breach shall be [***].

20.6 [***].

20.7 At such time as the Purchaser has remedied the Material CRE Breach in respect of the relevant Royalty Product, the Purchaser shall be entitled to terminate the [***] and the Purchaser's rights and obligations in respect of such Royalty Product shall continue in accordance with the terms of this Agreement.

20.8 The Purchaser's intention at all times when performing its obligations pursuant to this clause 20 shall be to ensure that it minimizes any disruptions to patients' accessing the Royalty Products. If, in the opinion of the Purchaser, there is a material risk to patient safety because of the procedure and timelines described in this clause 20.8, the time limits set out herein shall be deemed to reduce by [***] (so, for example, the [***] time limit in clause 20.3 shall be reduced to [***] in such circumstances).

20.9 For the avoidance of doubt, the Seller's sole recourse in respect of any breach of the Purchaser's obligations pursuant to clauses 5.2 (b), (c) and/or (d) shall be as set out in this clause 20 provided that this clause 20 shall not prevent or preclude the Purchaser from enforcing any other provision of this Agreement in any manner permitted in law or in equity.

Termination for Safety Reason

20.10 Termination for a Safety Reason

In the event that the Purchaser has a bona fide Significant Safety Concern or Other Safety Concern with respect to any Programme or any Royalty Product developed or in development thereunder it shall notify the Seller in writing as soon as reasonably practicable, setting out the factual basis for such concerns in reasonable detail. In such circumstances:

(a) if the safety concern is a Significant Safety Concern the Purchaser shall be entitled to terminate the development and/or commercialisation of the relevant Programme or Royalty Product and/or terminate the licence under the Telethon-HSR Agreement in so far as it relates to that Programme or Royalty Product;

(b) if the safety concern is an Other Safety Concern, the Purchaser shall be entitled to terminate the development and/or commercialisation of the relevant Programme or Royalty Product and/or to terminate the licence under the Telethon-HSR Agreement in so far as it relates to that Programme and or Royalty Product with the prior written consent of the Seller, not to be unreasonably withheld, conditioned or delayed.

Termination of a Programme(s) under the Telethon-HSR Agreement

20.11 On a Programme-by-Programme basis, in the event that either (a) the Purchaser terminates a Programme under the Telethon-HSR Agreement, or (b) Telethon-HSR terminates a Programme under Sections 12.2 (Termination for Cause), Section 12.3 (Termination Rights of Either Party for Safety Reasons), or Section 12.4 (Purchaser Insolvency) of the Telethon-HSR Agreement, then the licenses granted by the Seller to the Purchaser pursuant to clause 11.2 shall also terminate with immediate effect solely with respect to such terminated Programme.

20.12 In the event of a termination of a Programme in circumstances described in clause 20.11, then the covenants given by the Seller to the Purchaser pursuant to clause 14.1 shall also terminate with immediate effect solely with respect to such terminated Programme.

20.13 In the event of a termination of a Programme in circumstances described in clause 20.11, then the licence granted by the Purchaser to the Seller pursuant to clause 11.5(a)(ii) with respect to the Telethon-HSR Agreement for such terminated Programme shall also terminate with immediate effect solely to the extent that such Know-How was licensed to the Purchaser under the Telethon-HSR Agreement.

21. HUMAN BIOLOGICAL SAMPLE MANAGEMENT

21.1 The Purchaser will use any Human Biological Samples (including the Patient Samples) only for the purposes that are consistent with the applicable informed consent forms for such materials.

21.2 The Purchaser shall ensure that it has all the necessary authorisations, licenses, legal and/or regulatory consents (except for patient consents) and approvals (for example, ethical approval from an ethics committee, or as may be otherwise prescribed by applicable law) to obtain, collect, store, transfer, use (including subsequent use by a commercial organisation), disclose, import, export and dispose of any Human Biological Samples provided to the Purchaser under this Agreement.

21.3 The Purchaser will comply with and will continue to comply with all applicable laws and issued codes of practice and guidance relating to the collection, storage, use and disposal of Human Biological Samples.

22. MISCELLANEOUS

22.1 Further Assurances

Each party shall from time to time execute such documents and perform such acts and things as any party may reasonably require in order to give full effect to the provisions of this Agreement and the transactions contemplated by it.

22.2 Reasonableness

Each party to this Agreement confirms it has received independent legal advice relating to all the matters provided for in this Agreement, including the provisions of clauses 7 (*Responsibility for Liabilities*), 14 (*Restrictive Covenant*) and 24 (*Whole Agreement*), and agrees, having considered the terms of such clauses and the Agreement as a whole, that the provisions of such clauses and this Agreement are fair and reasonable.

22.3 Counterparts

This Agreement may be entered into in any number of counterparts all of which taken together shall constitute one and the same instrument. Any party may enter into this Agreement by executing any such counterpart. Delivery of a counterpart of this Agreement by email attachment shall be an effective mode of delivery.

23. VARIATION AND WAIVER

23.1 No variation of this Agreement shall be effective unless in writing and signed by or on behalf of each party.

23.2 No failure of either party to exercise, and no delay by it in exercising, any right, power or remedy in connection with this Agreement (each a "**Right**") shall operate as a waiver of that Right, nor shall any single or partial exercise of any Right preclude any other or further exercise of that Right or the exercise of any other Right.

24. WHOLE AGREEMENT

24.1 This Agreement, together with the other Transaction Documents, constitutes the entire agreement between the parties with respect to the subject matter of this Agreement and (to the extent permissible by applicable law) supersedes all prior representations or oral or written agreements between the parties with respect to that subject matter, provided that neither party is attempting to exclude any liability for fraudulent statements.

24.2 Each party acknowledges that it has not been induced to enter into this Agreement by any representation, warranty or undertaking not expressly incorporated into it.

24.3 To the maximum extent permitted by applicable law, all terms, conditions and warranties, other than those expressly set out in this Agreement, are excluded including all implied and statutory terms, warranties and conditions relating to satisfactory quality or fitness for purpose. If any legislation implies into this Agreement any term, condition or warranty which cannot be lawfully excluded then that term, condition or warranty shall be included in this Agreement to the extent required by the relevant legislation but each party's liability in respect of any breach thereof shall be limited to the maximum extent (if any) permitted by that legislation.

24.4 In this clause 24, references to "this Agreement" includes all other documents entered into pursuant to this Agreement.

25. DEFAULT INTEREST

25.1 If any party which is required to pay any sum under this Agreement fails to pay any sum payable by it under this Agreement on the due date for payment (the "**Defaulting Party**"), it shall pay interest on such sum at the Default Rate for the period from and including the due date up to the date of actual payment (after as well as before judgement) in accordance with this clause.

25.2 Interest under this clause 25 shall accrue on the basis of the actual number of days elapsed and a 365-day year and shall be paid by the Defaulting Party on demand. Unpaid interest shall compound monthly based on a 30-day month.

26. NOTICES

26.1 Save as otherwise provided in this Agreement, any notice, demand or other communication ("**Notice**") to be given by any party under, or in connection with, this Agreement or any of the other Transaction Documents shall be in writing and signed by or on behalf of the party giving it. Any Notice shall be served by sending it by pre-paid recorded delivery, registered post or delivering it by hand, in each case to the address set out in clause 26.2 and in each case marked for the attention of the relevant party set out in clause 26.2 (or as otherwise notified from time to time in accordance with the provisions of this clause 26.2). Any Notice so served by pre-paid recorded delivery, registered post or by hand shall be deemed to have been duly given or made as follows:

(a) in the case of pre-paid recorded delivery or registered post, 2 (two) Business Days after the date of posting; or

(b) in the case of delivery by hand, when delivered,

provided that in each case where delivery occurs after 6pm on a Business Day or on a day which is not a Business Day, service shall be deemed to occur at 9am on the next following Business Day. References to time in this clause are to local time in the country of the addressee.

26.2 The addresses of the parties for the purpose of clause 26.1 are as follows:

(a) Purchaser

Address:	Orchard Therapeutics Limited 108 Cannon Street, London, EC4N 6EU Attn: CEO With copies to: General Counsel and the SVP for Business Development
With copies to:	Cooley (UK) LLP Dashwood, 69 Old Broad Street London, EC2M 1QS [***]

(b) Seller

Address:	Glaxo Group Limited 980 Great West Road Brentford, Middlesex TW8 9GS, England Attn: Company Secretary GlaxoSmithKline Intellectual Property Development Ltd. 980 Great West Road Brentford, Middlesex TW8 9GS, England Attn: Company Secretary

With copies to: King & Spalding International LLP

125 Old Broad Street
London
EC2N 1AR
[***]

and

SVP BDTT, GSK Legal,
GSK House
980 Great West Road,
Brentford,
Middlesex, TW8 9GS,
England

26.3 A party may notify the other party to this Agreement of a change to its name, relevant addressee or address for the purposes of this clause 26, provided that such notice shall only be effective on:

(a) the date specified in the notification as the date on which the change is to take place; or

(b) if no date is specified or the date specified is less than 5 (five) Business Days after the date on which notice is given, the date following 5 (five) Business Days after notice of any change has been given.

26.4 In proving service it shall be sufficient to prove that the envelope containing such notice was properly addressed and delivered to the address shown thereon.

27. COSTS

Except as expressly provided in this Agreement, each of the parties shall be responsible for its own legal, accountancy and other costs, charges and expenses incurred in connection with the negotiation, preparation and implementation of this Agreement and any other Transaction Document.

28. RIGHTS OF THIRD PARTIES

The parties do not intend that any term of this Agreement shall be enforceable by virtue of the Contracts (Rights of Third Parties) Act 1999 by any person who is not a party to this Agreement.

29. CONTINUING EFFECT

Each provision of this Agreement shall continue in full force and effect after Completion (including but not limited to the Warranties), except to the extent that a provision has been fully performed on or before Completion.

30. ASSIGNMENT, SUBCONTRACTING

30.1 Except as provided in clauses 5.5 or 30.2, neither party may assign or transfer all or any of its rights or obligations under this Agreement or dispose of any right or interest in this Agreement without the prior written consent of the other party.

30.2 Subject to clause 5.5 either the Purchaser or the Seller shall be entitled to assign its rights or obligations under this Agreement to any of its Affiliates, provided that:

(a) the assigning party shall remain responsible for the performance of its obligations hereunder by any such Affiliate;

(b) the assigning party shall procure that any such Affiliate to which it assigns any of its rights under this Agreement shall assign such rights back to the assigning party immediately prior to it ceasing to be an Affiliate;

(c) the non-assigning party's liability to any assignee shall not be greater than if such assignment had not taken place; and

(d) the assigning party shall in advance of such assignment inform the other party where the assignee is both resident and has a business presence for Tax purposes for the purposes of enabling the other party to determine whether Tax must be withheld or deducted from any payment made under this Agreement and the place of any supply for VAT purposes.

30.3 Termination for a Safety Reason

In the event that the Purchaser has a bona fide Significant Safety Concern or Other Safety Concern with respect to any Programme or any Royalty Product developed or in development thereunder it shall notify the Seller in writing as soon as reasonably practicable, setting out the factual basis for such concerns in reasonable detail. In such circumstances:

(a) if the safety concern is a Significant Safety Concern the Purchaser shall be entitled to terminate the development and/or commercialisation of the relevant Programme or Royalty Product and/or terminate the licence under the Telethon-HSR Agreement in so far as it relates to that Programme or Royalty Product;

(b) if the safety concern is an Other Safety Concern, the Purchaser shall be entitled to terminate the development and/or commercialisation of the relevant Programme or Royalty Product and to terminate the licence under the Telethon-HSR Agreement in so far as it relates to that Programme and or Royalty Product with the prior written consent of the Seller, not to be unreasonably withheld, conditioned or delayed.

31. CURRENCY CONVERSION

For the purpose of converting amounts specified in one currency into another currency where required, the rate of exchange to be used shall be the closing mid-point rate for exchanges between those currencies quoted on www.oanda.com and, in the event such resource is no longer available, in the Financial Times (London edition) for the nearest Business Day for which that rate is so quoted on or prior to the date of the conversion.

32. GOVERNING LAW, APPOINTMENT OF EXPERT AND SUBMISSION TO JURISDICTION

32.1 Governing law

The construction, validity and performance of this Agreement and all non-contractual obligations arising from or connected with this Agreement shall be governed by English law.

32.2 Expert

An expert means any person appointed in accordance with this clause 32.2 to resolve any dispute pursuant to clause 5.2(f) or (g). The following terms shall apply:

(a) the parties shall co-operate in good faith to agree on the appointment of an Independent Third Party to act as an expert and to agree the terms of their appointment;

(b) if the parties fail to agree on the identity of the Expert by the date [***] from the date on which the Seller notifies the Purchaser, as relevant, in accordance with clause 5.2(f), that the Seller does not agree with the Product Market Proposal made by the Purchaser in accordance with that clause and/or in accordance with clause 5.2(g) that the Seller objects to a proposed deferment of the payment of the payment of royalties in accordance with that clause, either party may request the Chairman of the Institute of Chartered Accountants to appoint the Expert who shall be a person of repute with international experience in the type of matter in dispute;

(c) within [***] of the date of the appointment of the Expert, each party shall be entitled to make submissions to the Expert and will provide (or procure that others provide) the Expert with such assistance and documents as the Expert reasonably requires for the purpose of reaching a decision;

(d) the Expert shall be required to prepare a written decision and give notice of the decision to the parties within a maximum of [***] from the date on which the Expert receives submissions from both parties or the end of the period referred to in paragraph 32.2(c) above if no submission is made by either or both parties;

(e) to the extent not provided for in this clause 32, the Expert may in its reasonable discretion determine such other procedures to assist with the conduct of the determination as he considers just or appropriate;

(f) the Expert shall act as an expert and not an arbitrator. The Expert's decision shall be final and binding on the parties in the absence of manifest error or fraud; and

(g) the costs and expenses of the Expert shall be shared equally between the parties unless the Expert determines otherwise.

32.3 Dispute Resolution

The parties agree to adhere to the following procedure in respect of any Dispute:

(a) Any Dispute must in the first instance be referred by either the Seller or the Purchaser to the Senior Managers. The Senior Managers shall meet within [***] of escalation of the matter to them to discuss and attempt to resolve the issue, acting reasonably and in good faith. If, however, after good faith attempts to reach agreement to resolve such issue, the Senior Managers are unable to reach agreement within [***] of their initial meeting to discuss the issue (or if the Senior Managers fail to meet for whatever reason, within [***] of the referral to the Senior Managers), then either party may submit such matter to dispute resolution as set out below.

(b) Any Dispute may be referred by either party to arbitration under the rules of London Court of International Arbitration (the "**Rules**") for final resolution, which Rules are deemed to be incorporated by reference into this clause. In any arbitration commenced pursuant to this Agreement, the number of arbitrators shall be three who shall be appointed in accordance with the Rules. The seat of the arbitration shall be London, England and the language of the arbitration shall be English.

(c) At any time prior to or after the commencement of an arbitration in accordance with this clause, either party may apply to relevant courts for purposes of obtaining interim relief, including, without limitation, any interim injunction. Where a party seeks such interim relief after commencement of the arbitration, and the case is not one of urgency, that party shall act only with the permission of the arbitral tribunal or the Agreement in writing of the other parties to the arbitration.

(d) Each party hereby consents generally in respect of any Proceedings to the giving of any relief or the issue of any process in connection with such Proceedings including the making, enforcement or execution against any property (irrespective of its use or intended use).

33. INVALIDITY

33.1 If any provision in this Agreement shall be held to be illegal, invalid or unenforceable, in whole or in part, the provision shall apply with whatever deletion or modification is necessary so that the provision is legal, valid and enforceable and gives effect to the commercial intention of the Parties.

33.2 To the extent it is not possible to delete or modify the provision, in whole or in part, under clause 32.1 then such provision or part of it shall, to the extent that it is illegal, invalid or unenforceable, be deemed not to form part of this Agreement and the legality, validity and enforceability of the remainder of this Agreement shall, subject to any deletion or modification made under clause 32.1, not be affected.

34. GOVERNING LANGUAGE

The official text of the Transaction Documents and any notices given thereunder shall be in English. In the event of any dispute concerning the construction or interpretation of any Transaction Document, reference shall be made only to the relevant Transaction Document as written in English and not to any translation into any other language.

The parties have shown their acceptance of the terms of this Agreement by executing it at the end of the Schedules.

IN WITNESS WHEREOF the Parties have signed this Agreement on the date stated above.

SIGNED by	)
	)
/s/ John Sadler	)
duly authorised for and on behalf	)
of **Glaxo Group Limited**	)
SIGNED by	)
	)
/s/ John Sadler	)
duly authorised for and on behalf	)
of **GlaxoSmithKline Intellectual Property Development Ltd.**	)
SIGNED by	)
	)
	)
duly authorised for and on behalf	)
of **Orchard Therapeutics Limited**	)

IN WITNESS WHEREOF the Parties have signed this Agreement on the date stated above.

SIGNED by)
)
)
duly authorised for and on behalf)
of **Glaxo Group Limited**)

SIGNED by)
)
)
duly authorised for and on behalf)
of **GlaxoSmithKline Intellectual Property Development Ltd.**)

SIGNED by)
)
/s/ Mark Rothera)
duly authorised for and on behalf)
of **Orchard Therapeutics Limited**)

The Companies Act 2006
Public Company Limited by shares

ARTICLES OF ASSOCIATION

of

ORCHARD THERAPEUTICS PLC

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Company number: 11494381

NEW

ARTICLES OF ASSOCIATION

of

ORCHARD THERAPEUTICS PLC (the "Company")

1 **Defined terms**

1.1 No regulations or articles set out in any statute, or in any statutory instrument or other subordinate legislation made under any statute, concerning companies (including the regulations in the Companies (Model Articles) Regulations 2008 (SI 2008/3229)) shall apply as the articles of the Company. The following shall be the articles of association of the Company.

2 **Interpretation**

2.1 In these Articles, the following words and expressions shall have the meanings set out below:

"**Act**" means the Companies Act 2006

"**address**" includes any number or address used for the purposes of sending or receiving documents or information by electronic means

"**Articles**" means these articles of association as altered from time to time and Article shall be construed accordingly

"**Board**" means the board of Directors for the time being of the Company or the Directors present or deemed to be present at a duly convened quorate meeting of the Directors

"**certificated shares**" a share which is not an uncertificated share and references in these Articles to a share being held in certificated form shall be construed accordingly

"**clear days**" in relation to a period of notice means that period excluding the day when the notice is served or deemed to be served and the day for which it is given or on which it is to take effect

"**Companies Acts**" means the Act, the Companies Act 1985 and, where the context requires, every other statute from time to time in force concerning companies and affecting the Company

"**Deferred Shares**" has the meaning given to it in Article 4

"**Director**" means a director for the time being of the Company

"**FSMA**" means the Financial Services and Markets Act 2000

"**electronic form**" has the meaning given to it in section 1168 of the Act

"**electronic means**" has the meaning given to it in section 1168 of the Act

"**Listing**" means the listing of the Company's Ordinary Shares (in the form of American depositary shares) on NASDAQ

"**member**" means a member of the Company, or where the context requires, a member of the Board or of any committee

"**NASDAQ**" means The NASDAQ Stock Market LLC

"**NASDAQ Rules**" means the rules of NASDAQ

"**Office**" means the registered office from time to time of the Company

"**Operator**" means Euroclear UK and Ireland Limited or such other person as may for the time being be approved by HM Treasury as Operator under the uncertificated securities rules

"**Ordinary Shares**" has the meaning given to it in Article 4

"**paid up**" means paid up or credited as paid up

"**participating class**" means a class of shares title to which is permitted by the Operator to be transferred by means of a relevant system.

"**Register**" means the register of members of the Company to be maintained under the Act or as the case may be any overseas branch register maintained under Article 117

"**relevant system**" means a computer-based system which allows units of securities without written instruments to be transferred and endorsed pursuant to the uncertificated securities rules

"**Seal**" means the common seal of the Company or, where the context allows, any official seal kept by the Company under section 50 of the Act

"**Secretary**" means the secretary of Company for the time being;

"**Share Warrant**" means a warrant to bearer issued by the Company in respect of its shares

"**uncertificated securities rules**" means any provision of the Companies Acts relating to the holding, evidencing of title to, or transfer of uncertificated shares and any legislation, rules or other arrangements made under or by virtue of such provision (including the Uncertificated Securities Regulations 2001 as amended or replaced from time to time and any subordinate legislation or rules made under them for them time being in force)

"**uncertificated share**" means a share of a class which is at the relevant time a participating class, title to which is recorded on the Register as being held in uncertificated form and references in these Articles to a share being held in uncertificated form shall be construed accordingly

2.2 Headings are used for convenience only and shall not affect the construction or interpretation of these Articles.

2.3 A **person** includes a corporate and an unincorporated body (whether or not having separate legal personality).

2.4 Words in the singular shall include the plural and vice versa.

2.5 A reference to one gender shall include a reference to the other gender.

2.6 A reference to a statute or statutory provision is a reference to it as it is in force for the time being, taking account of any amendment, extension, or re-enactment and includes any subordinate legislation for the time being in force made under it.

2.7 Any words or expressions defined in the Companies Acts in force when these Articles or any part of these Articles are adopted shall (if not inconsistent with the subject or context in which they appear) have the same meaning in these Articles or that part, save that the word **company** shall include any body corporate.

2.8 A reference to a document **being signed** or to **signature** includes references to its being executed under hand or under seal or by any other method and, in the case of a communication in electronic form, such references are to its being authenticated as specified by the Companies Acts.

2.9 A reference to **writing** or **written** includes references to any method of representing or reproducing words in a legible and non-transitory form whether sent or supplied in electronic form or otherwise.

2.10 A reference to documents or information **being sent or supplied by or to** a company (including the Company) shall be construed in accordance with section 1148(3) of the Act.

2.11 A reference to a **meeting** shall not be taken as requiring more than one person to be present if any quorum requirement can be satisfied by one person.

2.12 If any Article (or part thereof) is or becomes inconsistent with any laws or regulations of any country to which affairs of the Company are subject such laws or regulations shall prevail and the relevant Article (or part thereof) shall be construed accordingly.

3 Form of Resolution

Subject to the Companies Acts, where anything can be done by passing an ordinary resolution, this can also be done by passing a special resolution.

4 Capital

The capital of the Company is divided into an unlimited number of ordinary shares of £0.10 pence each ("**Ordinary Shares**") and an unlimited number of deferred shares of £4.89687 pence each ("**Deferred Shares**") conferring on the holders the rights and being subject to the restrictions set out in this Article 10.

5 Limited Liability

The liability of the members of the Company is limited to the amount, if any, unpaid on the shares in the Company held by them.

6 Change of Name

The Company may change its name by resolution of the Board.

7 Power to Attach Rights to Shares

Subject to the Companies Acts and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the Company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the Board may determine.

8 **Allotment of Shares and Pre-Emption**

8.1 Subject to the Companies Acts, these Articles and to any relevant authority of the Company in general meeting required by the Act, the Board may offer, allot (with or without conferring rights of renunciation), grant options over or otherwise deal with or dispose of shares or grant rights to subscribe for or convert any security into shares to such persons, at such times and upon such terms as the Board may decide. No share may be issued at a discount.

8.2 The Board may, at any time after the allotment of any share but before any person has been entered in the Register, recognise a renunciation by the allottee in favour of some other person and accord to the allottee of a share a right to effect such renunciation and/or allow the rights to be represented to be one or more participating securities, in each case upon and subject to such terms and conditions as the Board may think fit to impose.

8.3 Under and in accordance with section 551 of the Act, the Directors shall be generally and unconditionally authorised to exercise for each prescribed period all the powers of the Company to allot shares up to an aggregate nominal amount equal to the Section 551 Amount (as defined below).

8.4 Under and within the terms of the said authority or otherwise in accordance with section 570 of the Act, the Directors shall be empowered during each prescribed period to allot equity securities (as defined by the Act) wholly for cash:

(a) in connection with a rights issue; and

(b) otherwise than in connection with a rights issue up to an aggregate nominal amount equal to the Section 561 Amount (as defined below).

8.5 During each prescribed period the Company and its Directors by such authority and power may make offers or agreements which would or might require equity securities or other securities to be allotted after the expiry of such period.

8.6 For the purposes of this Article 8:

(a) **rights issue** means an offer of equity securities (as defined by the Act) open for acceptance for a period fixed by the Board to holders of equity securities on the Register on a fixed record date in proportion to their respective holdings of such securities or in accordance with the rights attached to them but subject to such exclusions or other arrangements as the Board may deem necessary or expedient with regard to treasury shares, fractional entitlements or legal or practical problems under the laws of any territory or under the requirements of any recognised regulatory body or stock exchange in any territory;

(b) **prescribed period** means any period (not exceeding five years on any occasion) for which the authority, in the case of Article 8.3, is conferred or renewed by ordinary or special resolution stating the Section 551 Amount and in the case of Article 8.4 is conferred or renewed by special resolution stating the Section 561 Amount;

(c) **Section 551 Amount** means for any prescribed period, the amount stated in the relevant ordinary or special resolution;

(d) **Section 561 Amount** means for any prescribed period, the amount stated in the relevant special resolution; and

(e) the nominal amount of any securities shall be taken to be, in the case of rights to subscribe for or to convert any securities into shares of the Company, the nominal amount of such shares which may be allotted pursuant to such rights.

9 **Redeemable Shares**

Subject to the Companies Acts and to any rights attaching to existing shares, any share may be issued which can be redeemed or is liable to be redeemed at the option of the Company or the holder. The Board may determine the terms, conditions and manner of redemption of any redeemable shares which are issued. Such terms and conditions shall apply to the relevant shares as if the same were set out in these Articles.

10 **Shareholder Rights**

10.1 The Ordinary Shares shall rank pari passu as a single class. The Deferred Shares shall rank pari passu as a single class.

10.2 In the event of the liquidation, dissolution or winding up of the Company, the assets of the Company available for distribution to members shall be distributed amongst all holders of the Ordinary Shares in proportion to the number of shares held irrespective of the amount paid or credited as paid on any share.

10.3 Any:

(a) consolidation or merger of the Company with or into another entity or entities (whether or not the Company is the surviving entity) as a result of which the holders of the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board immediately prior to such sale or issue cease to own the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board;

(b) sale or transfer by the Company of all or substantially all of its assets (determined either for the Company alone or together with its subsidiaries on a consolidated basis); or

(c) sale, transfer or issuance or series of sales, transfers and/or issues of shares by the Company or the holders thereof, as a result of which the holders of the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board immediately prior to such sale or issue cease to own the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board,

shall be deemed to be a liquidation, dissolution and winding up of the Company for purposes of Article 10.2 (unless the Board determine otherwise), and the holders of the Ordinary Shares shall be entitled to receive from the Company the amounts payable with respect to the Ordinary Shares on a liquidation, dissolution or winding up of the Company under Article 10.2 in cancellation of their Ordinary Shares upon the completion of any such transaction.

10.4 At a general meeting of the Company and at any separate class meeting of the holders of Ordinary Shares, where a holder of Ordinary Shares is entitled to vote, such holder is entitled to one vote for each Ordinary Share held.

10.5 A holder of Ordinary Shares is entitled to receive notice of any general meeting of the Company (and notice of any separate class meeting of the holders of Ordinary Shares) and a copy of every report, accounts, circular or other document sent out by the Company to members.

10.6 Notwithstanding any other provision of these Articles, the special rights, privileges, restrictions and limitations attaching to the Deferred Shares are as follows:

(a) the Deferred Shares shall not be entitled to any dividends or to any other right or participation in the profits of the Company;

(b) on return of assets on liquidation, the Deferred Shares shall confer on the holders thereof an entitlement to receive out of the assets of the Company available for distribution amongst the members (subject to the rights of any new class of shares with preferred rights) the amount paid up or credited as paid up on the deferred shares held by them respectively after (but only after) payment shall have been made to the holders of the Ordinary Shares of the amounts paid up or credited as paid up on such shares and the sum of £1,000,000 in respect of each Ordinary Share held by them respectively. The Deferred Shares shall confer on the holders thereof no further right to participate in the assets of the Company;

(c) the Deferred Shares do not entitle the holder thereof to vote upon any resolution or to receive notice of, attend any general meeting, or be part of the quorum thereof as the holders of the Deferred Shares;

(d) any reduction of capital involving the cancellation of the Deferred Shares for no consideration shall not be deemed to be a variation of the rights attaching to them nor a modification or abrogation of the rights or privileges attaching to the Deferred Shares;

(e) the special rights conferred upon the holders of the Deferred Shares shall be deemed not to be modified, varied or abrogated by the creation or issue of further shares ranking pari passu with or in priority to the Deferred Shares;

(f) the Deferred Shares shall not be entitled to be reissued with a share certificate;

(g) no transfer of any Deferred Shares shall be permitted save as provided in Article 10.6(h);

(h) the Company shall have irrevocable authority at any time to appoint any person to execute on behalf of the holders of the Deferred Shares a transfer thereof and/or an agreement to transfer the same, without making any payment to the holders thereof, or to such person as the Company may determine as custodian thereof and/or to cancel the same without making any payment to the holders thereof and/or acquire the same (in accordance with the provisions of the Act) without making any payment to or obtaining the sanction of the holders thereof; and

(i) subject to the Act, the Company shall be entitled to purchase any Deferred Shares in issue at any time for no consideration.

11 **Pari Passu Issues**

If new shares are created or issued which rank equally with any other existing shares, the rights of the existing shares will not be regarded as changed or abrogated unless the terms of the existing shares expressly say otherwise.

12 **Variation of Rights**

12.1 Subject to the Companies Acts, the rights attached to any class of shares can be varied or abrogated either with the consent in writing of the holders of not less than three-quarters in nominal value of the issued share of that class (excluding any shares of that class held as treasury shares) or with the authority of a special resolution passed at a separate meeting of the holders of the relevant class of shares known as a **class meeting**.

12.2 The provisions of this Article will apply to any variation or abrogation of rights of shares forming part of a class. Each part of the class which is being treated differently is treated as a separate class in applying this Article.

12.3 All the provisions in these Articles as to general meetings shall apply, with any necessary modifications, to every class meeting except that:

(a) the quorum at every such meeting shall not be less than two persons holding or representing by proxy at least one-third of the nominal amount paid up on the issued shares of the class) (excluding any shares of that class held as treasury shares); and

(b) if at any adjourned meeting of such holders such quorum as set out above is not present, at least one person holding shares of the class who is present in person or by proxy shall be a quorum.

12.4 The Board may convene a class meeting whenever it thinks fit and whether or not the business to be transacted involves a variation or abrogation of class rights.

13 **Payment of Commission**

The Company may in connection with the issue of any shares or the sale for cash of treasury shares exercise all powers of paying commission and brokerage conferred or permitted by the Companies Acts. Any such commission or brokerage may be satisfied by the payment of cash or by the allotment of fully or partly paid shares or other securities or the grant of an option to call for an allotment of shares or any combination of such methods.

14 **Trusts Not Recognised**

Except as otherwise expressly provided by these Articles, required by law or as ordered by a court of competent jurisdiction, the Company shall not recognise any person as holding any share on any trust, and the Company shall not be bound by or required in any way to recognise (even when having notice of it) any equitable, contingent, future, partial or other claim to or interest in any share other than an absolute right of the holder of the whole of the share.

15 **Uncertificated Shares**

15.1 Under and subject to the uncertificated securities rules, the Board may permit title to shares of any class to be evidenced otherwise than by certificate and title to shares of such a class to be transferred by means of a relevant system and may make arrangements for a class of shares (if all shares of that class are in all respects identical) to become a participating class. Title to shares of a particular class may only be evidenced otherwise than by a certificate where that class of shares is at the relevant time a participating class. The Board may also, subject to compliance with the uncertificated securities rules, determine at any time that title to any class of shares may from a date specified by the Board no longer be evidenced otherwise than by a certificate or that title to such a class shall cease to be transferred by means of any particular relevant system.

15.2 In relation to a class of shares which is a participating class and for so long as it remains a participating class, no provision of these Articles shall apply or have effect to the extent that it is inconsistent in any respect with:

(a) the holding of shares of that class in uncertificated form;

(b) the transfer of title to shares of that class by means of a relevant system; or

(c) any provision of the uncertificated securities rules,

and, without prejudice to the generality of this Article, no provision of these Articles shall apply or have effect to the extent that it is in any respect inconsistent with the maintenance, keeping or entering up by the Operator, so long as that is permitted or required by the uncertificated securities rules, of an Operator register of securities in respect of that class of shares in uncertificated form.

15.3 Ordinary Shares of a class which is at the relevant time a participating class may be changed from uncertificated to certificated form, and from certificated to uncertificated form, in accordance with and subject as provided in the uncertificated securities rules.

15.4 If, under these Articles or the Companies Acts, the Company is entitled to sell, transfer or otherwise dispose of, forfeit, re-allot, accept the surrender of or otherwise enforce a lien over an uncertificated share, then, subject to these Articles and the Companies Acts, such entitlement shall include the right of the Board to:

(a) require the holder of the uncertificated share by notice in writing to change that share from uncertificated to certificated form within such period as may be specified in the notice and keep it as a certificated share for as long as the Board requires;

(b) appoint any person to take such other steps, by instruction given by means of a relevant system or otherwise, in the name of the holder of such share as may be required to effect the transfer of such share and such steps shall be as effective as if they had been taken by the registered holder of that share; and

(c) take such other action that the Board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of that share or otherwise to enforce a lien in respect of that share.

15.5 Unless the Board determines otherwise, shares which a member holds in uncertificated form shall be treated as separate holdings from any shares which that member holds in certificated form but a class of shares shall not be treated as two classes simply because some shares of that class are held in certificated form and others in uncertificated form.

15.6 Unless the Board determines otherwise or the uncertificated securities rules require otherwise, any shares issued or created out of or in respect of any uncertificated shares shall be uncertificated shares and any shares issued or created out of or in respect of any certificated shares shall be certificated shares.

15.7 The Company shall be entitled to assume that the entries on any record of securities maintained by it in accordance with the uncertificated securities rules and regularly reconciled with the relevant Operator register of securities are a complete and accurate reproduction of the particulars entered in the Operator register of securities and shall accordingly not be liable in respect of any act or thing done or omitted to be done by or on behalf of the Company in reliance on such assumption. Any provision of these Articles which requires or envisages that action will be taken in reliance on information contained in the Register shall be construed to permit that action to be taken in reliance on information contained in any relevant record of securities (as so maintained and reconciled).

16 **Share Certificates**

16.1 Every person (except a person to whom the Company is not by law required to issue a certificate) whose name is entered in the Register as a holder of any certificated shares shall be entitled, without charge, to receive within the time limits prescribed by the Companies Acts (unless the terms of issue prescribe otherwise) one certificate for all of the shares of that class registered in his name.

16.2 The Company shall not be bound to issue more than one certificate in respect of shares held jointly by two or more persons. Delivery of a certificate to the person first named in the Register shall be sufficient delivery to all joint holders.

16.3 Where a member has transferred part only of the shares comprised in a certificate, he shall be entitled without charge to a certificate for the balance of such shares to the extent that the balance is to be held in certificated form. Where a member receives more shares of any class, he shall be entitled without charge to a certificate for the extra shares of that class to the extent that the balance is to be held in certificated form.

16.4 A share certificate may be issued under Seal (by affixing the Seal to or printing the Seal or a representation of it on the certificate) or signed by at least two Directors or by at least one Director and the Secretary. Such certificate shall specify the number and class of the shares in respect of which it is issued and the amount or respective amounts paid up on it. The Board may be resolution decide, either generally or in any particular case or cases, that any signatures on any share certificates need not be autographic but may be applied to the certificates by some mechanical or other means or may be printed on them or that the certificates need not be signed by any **person**.

16.5 Every share certificate sent in accordance with these Articles will be sent at the risk of the member or other person entitled to the certificate. The Company will not be responsible for any share certificate lost or delayed in the course of delivery.

16.6 No share certificates shall be issued in respect of the Deferred Shares.

17 Replacement Certificates

17.1 Any two or more certificates representing shares of any one class held by any member may at his request be cancelled and a single new certificate for such shares issued in lieu without charge on surrender of the original certificates for cancellation.

17.2 Any certificate representing shares of any one class held by any member may at his request be cancelled and two or more certificates for such shares may be issued instead.

17.3 If a share certificate is defaced, worn out or said to be stolen, lost or destroyed, it may be replaced on such terms as to evidence and indemnity as the Board may decide and, where it is defaced or worn out, after delivery of the old certificate to the Company.

17.4 The Board may require the payment of any exceptional out-of-pocket expenses of the Company incurred in connection with the issue of any certificates under this Article. In the case of shares held jointly by several persons, any such request as is mentioned in this Article may be made by any one of the joint holders.

18 Lien on Shares not Fully Paid

The Company shall have a first and paramount lien on every share, not being a fully paid share, for all amounts payable to the Company (whether presently or not) in respect of that share. The Company's lien over a share takes priority over any third party's interest in that share, and extends to any dividend or other money payable by the Company in respect of that share (and, if the lien is enforced and the share is sold by the Company, the proceeds of sale of that share). The Board may at any time, either generally or in any particular case, waive any lien that has arisen or declare any share to be wholly or in part exempt from the provisions of this Article.

19 Enforcement of Lien by Sale

The Company may sell, in such manner as the Board may decide, any share over which the Company has a lien if a sum in respect of which the lien exists is presently payable and is not paid within 14 clear days after a notice has been served on the holder of the share or the person who is entitled by transmission to the share, demanding payment and stating that if the notice is not complied with the share may be sold. For giving effect to the sale, in the case of a certificated share, the Board may authorise some person to sign an instrument of transfer of the share sold to, or in accordance with the directions, of the buyer. In the case of an uncertificated share, the Board may require the Operator to convert the share into certificated form and after such conversion, authorise any person to sign the instrument of transfer of the share to affect the sale of the share. The buyer shall not be bound to see to the application of the purchase money, nor shall his title to the share be affected by any irregularity or invalidity in the proceedings in reference to the sale.

20 **Application of Proceeds of Sale**

The net proceeds of any sale of shares subject to any lien, after payment of the costs, shall be applied:

(a) first, in or towards satisfaction of so much of the amount due to the Company or of the liability or engagement (as the case may be) as is presently payable or is liable to be presently fulfilled or discharged; and

(b) second, any residue shall be paid to the person who was entitled to the share at the time of the sale but only after the certificate for the shares sold has been surrendered to the company for cancellation, or an indemnity in a form reasonably satisfactory to the directors has been given for any lost certificates, and subject to a like lien for debts or liabilities not presently payable as existed on the share prior to the sale.

21 **Calls**

21.1 Subject to these Articles and the terms on which the shares are allotted, the Board may from time to time make calls on the members in respect of any monies unpaid on their shares (whether in respect of nominal value or premium) and not payable on a date fixed by or in accordance with the terms of issue.

21.2 Each member shall (subject to the Company serving upon him at least 14 clear days' notice specifying when and where payment is to be made and whether or not by instalments) pay to the Company as required by the notice the amount called on for his shares.

21.3 A call shall be deemed to have been made at the time when the resolution of the Board authorising the call was passed.

21.4 A call may be revoked or postponed, in whole or in part, as the Board may decide.

21.5 Liability to pay a call is not extinguished or transferred by transferring the shares in respect of which the call is required to be paid.

22 **Liability of Joint Holders**

The joint holders of a share shall be jointly and severally liable to pay all calls in respect of the share.

23 **Interest on Calls**

If a call remains unpaid after it has become due and payable, the person from whom it is due and payable shall pay all expenses that have been incurred by the Company by reason of such non-payment together with interest on the amount unpaid from the day it is due and payable to the time of actual payment at such rate (not exceeding the Bank of England base rate by more than five percentage points) as the Board may decide. The Board may waive payment of the interest or the expenses in whole or in part.

24 **Power to Differentiate**

On or before the issue of shares, the Board may decide that allottees or holders of shares can be called on to pay different amounts or that they can be called on at different times.

25 **Payment of Calls in Advance**

The Board may, if it thinks fit, receive from any member willing to advance the same, all or any part of the monies uncalled and unpaid on the shares held by him. Such payment in advance of calls shall, to the extent of the payment, extinguish the liability on the shares on which it is made. The Company may pay interest on the money paid in advance, or so much of it as exceeds the amount for the time being called upon the shares in respect of which such advance has been made, at such rate as the Board may decide. The Board may at any time repay the amount so advanced by giving at least three months' notice in writing to such member of its intention to do so, unless before the expiration of such notice the amount so advanced shall have been called up on the shares in respect of which it was advanced.

26 **Notice if Call or Instalment Not Paid**

If any member fails to pay the whole of any call (or any instalment of any call) by the date when payment is due, the Board may at any time give notice in writing to such member (or to any person entitled to the shares by transmission), requiring payment of the amount unpaid (and any accrued interest and any expenses incurred by the Company by reason of such non-payment) by a date not less than 14 clear days from the date of the notice. The notice shall name the place where the payment is to be made and state that, if the notice is not complied with, the shares in respect of which such call was made will be liable to be forfeited.

27 **Forfeiture for Non-Compliance**

If the notice referred to in Article 26 is not complied with, any share for which it was given may be forfeited, by resolution of the Board to that effect, at any time before the payment required by the notice has been made. Such forfeiture shall include all dividends declared or other monies payable in respect of the forfeited shares and not paid before the forfeiture.

28 **Notice After Forfeiture**

When any share has been forfeited, notice of the forfeiture shall be served on the holder of the share or the person entitled to such share by transmission (as the case may be) before forfeiture. An entry of such notice having been given and of the forfeiture and the date of forfeiture shall immediately be made in the Register in respect of such share. However, no forfeiture shall be invalidated by any omission to give such notice or to make such entry in the Register.

29 **Forfeiture May Be Annulled**

The Board may annul the forfeiture of a share, at any time before any forfeited share has been cancelled or sold, re-allotted or otherwise disposed of, on the terms that payment shall be made of all calls and interest due on it and all expenses incurred in respect of the share and on such further terms (if any) as the Board shall see fit.

30 **Surrender**

The Board may accept the surrender of any share liable to be forfeited and, in any event, references in these Articles to forfeiture shall include surrender.

31 **Sale of Forfeited Shares**

31.1 A forfeited share shall become the property of the Company.

31.2 Subject to the Companies Acts, any such share may be sold, re-allotted or otherwise disposed of, on such terms and in such manner as the Board thinks fit.

31.3 The Board may, for the purposes of the disposal, authorise some person to transfer the share in question and may enter the name of the transferee in respect of the transferred share in the Register even if no share certificate is lodged and may issue a new certificate to the transferee. An instrument of transfer executed by that person shall be as effective as if it had been executed by the holder of or the person entitled by transmission to, the share. The Company may receive the consideration (if any) given for the share on its disposal.

32 **Effect of Forfeiture**

A member whose shares have been forfeited shall cease to be a member in respect of such forfeited shares and shall surrender the certificate for such shares to the Company for cancellation. Such member shall remain liable to pay to the Company all sums which at the date of forfeiture were presently payable by him to the Company in respect of such shares with interest (not exceeding the Bank of England base rate by two percentage points) from the date of the forfeiture to the date of payment. The Directors may waive payment of interest wholly or in part and may enforce payment, without any reduction or allowance for the value of the shares at the time of forfeiture or for any consideration received on their disposal.

33 **Evidence of Forfeiture**

A statutory declaration by a Director or the Secretary that a share has been forfeited on a specified date shall be conclusive evidence of the facts stated in it as against all persons claiming to be entitled to the share. The declaration shall (subject to the execution of an instrument of transfer if necessary) constitute a good title to the share. The person to whom the share is transferred or sold shall not be bound to see to the application of the purchase money or other consideration (if any), nor shall his title to the share be affected by any act, omission or irregularity relating to or connected with the proceedings in reference to the forfeiture or disposal of the share.

34 **Form of Transfer**

34.1 Subject to these Articles:

(a) each member may transfer all or any of his shares which are in certificated form by instrument of transfer in writing in any usual form or in any form approved by the Board. Such instrument shall be executed by or on behalf of the transferor and (in the case of a transfer of a share which is not fully paid up) by or on behalf of the transferee. All instruments of transfer, when registered, may be retained by the Company.

(b) each member may transfer all or any of his shares which are in uncertificated form by means of a relevant system in such manner provided for, and subject as provided in, the uncertificated securities rules. No provision of these Articles shall apply in respect of an uncertificated share to the extent that it requires or contemplates the effecting of a transfer by an instrument in writing or the production of a certificate for the share to be transferred.

34.2 The transferor of a share shall be deemed to remain the holder of the share concerned until the name of the transferee is entered in the Register in respect of it.

35 **Right to Refuse Registration of Transfer**

35.1 The Board may, in its absolute discretion, refuse to register any transfer of a share in certificated form (or renunciation of a renounceable letter of allotment) unless:

(a) it is for a share which is fully paid up;

(b) it is for a share upon which the Company has no lien;

(c) it is only for one class of share;

(d) it is in favour of a single transferee or no more than four joint transferees;

(e) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the Board to be exempt from stamp duty (if this is required); and

(f) is delivered for registration to the Office (or such other place as the Board may determine), accompanied (except in the case of a transfer by a person to whom the Company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the Board may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

35.2 The Board shall not refuse to register any transfer or renunciation of partly paid shares which are admitted to, or for which certificated or uncertificated depositary instruments over such shares are admitted to, NASDAQ on the grounds that they are partly paid shares in circumstances where such refusal would prevent dealings in such shares from taking place on an open and proper basis.

35.3 Transfers of shares will not be registered in the circumstances referred to in Article 72.

35.4 The Board may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the uncertificated securities rules and the relevant system.

36 **Notice of Refusal to Register a Transfer**

If the Board refuses to register a transfer of a share it shall notify the transferee of the refusal and the reasons for it within two months after the date on which the transfer was lodged with the Company or the instructions to the relevant system received. Any instrument of transfer which the Board refuses to register shall be returned to the person depositing it (except if there is suspected or actual fraud). All instruments of transfer which are registered may be retained by the Company.

37 **No Fees on Registration**

No fee shall be charged for registration of a transfer or other document or instruction relating to or affecting the title to any share or for making any other entry in the Register.

38 **Other Powers in Relation to Transfers**

Nothing in these Articles shall prevent the Board:

(a) from recognising a renunciation of the allotment of any share by the allottee in favour of another person; or

(b) (if empowered to do so by these Articles) from authorising any person to execute an instrument of transfer of a share and from authorising any person to transfer that share in accordance with any procedures implemented under Article 19.

39 **Transmission of Shares on Death**

If a member dies, the survivors or survivor (where he was a joint holder), and his executors or administrators (where he was a sole or the only survivor of joint holders), shall be the only persons recognised by the Company as having any title to his shares. Nothing in these Articles shall release the estate of a deceased member from any liability for any share which has been solely or jointly held by him.

40 **Election of Person Entitled By Transmission**

40.1 Any person becoming entitled to a share because of the death or bankruptcy of a member, or otherwise by operation of law, may (on such evidence as to his title being produced as the Board may require) elect either to become registered as a member or to have some person nominated by him registered as a member. If he elects to become registered himself, he shall

notify the Company to that effect. If he elects to have some other person registered, he shall execute an instrument of transfer of such share to that person. All the provisions of these Articles relating to the transfer of shares shall apply to the notice or instrument of transfer (as the case may be) as if it were an instrument of transfer executed by the member and his death, bankruptcy or other event had not occurred. Where the entitlement of a person to a share because of the death or bankruptcy of a member or otherwise by operation of law is proved to the satisfaction of the Board, the Board shall within 30 days after proof cause the entitlement of that person to be noted in the Register.

40.2 A person entitled by transmission to a share in uncertificated form who elects to have some other person registered shall either:

(a) procure that instructions are given by means of the relevant system to effect transfer of such uncertificated share to that person; or

(b) change the uncertificated share to certificated form and execute an instrument of transfer of that certificated share to that person.

41 **Rights on Transmission**

Where a person becomes entitled to a share because of the death or bankruptcy of any member, or otherwise by operation of law, the rights of the holder in relation to such share shall cease. However, the person so entitled may give a good discharge for any dividends and other monies payable in respect of it and shall have the same rights to which he would be entitled if he were the holder of the share, except that he shall not be entitled to receive notice of, or to attend or vote at, any meeting of the Company or any separate meeting of the holders of any class of shares of the Company before he is registered as the holder of the share. The Board may at any time give notice requiring any such person to elect either to be registered himself or to transfer the share. If the notice is not complied with within 30 days, the Board may withhold payment of all dividends and the other monies payable in respect of such share until the requirements of the notice have been complied with.

42 **Destruction of Documents**

42.1 The Company may destroy any:

(a) instrument of transfer, after six years from the date on which it is registered;

(b) dividend mandate or any variation or cancellation of a dividend mandate or any notification of change of name or address, after two years from the date on which it is recorded;

(c) share certificate, after one year from the date on which it is cancelled;

(d) instrument of proxy which has been used for the purpose of a poll at any time after one year has elapsed from the date of use;

(e) instrument of proxy which has not been used for the purpose of a poll at any time after a period of one month has elapsed from the end of the meeting to which the instrument of proxy relates;

(f) Share Warrant (including coupons or tokens detailed from it) which has been cancelled at any time after seven years from the date on which it was cancelled; or

(g) other document for which any entry in the Register is made, after six years from the date on which an entry was first made in the Register in respect of it,

provided that the Company may destroy any such type of document at a date earlier than that authorised by this Article if a copy of such document is made and retained (whether electronically, by microfilm, by digital imaging or by other similar means) until the expiration of the period applicable to the destruction of the original of such document.

42.2 It shall be conclusively presumed in favour of the Company that every:

(a) entry in the Register purporting to have been made on the basis of a document so destroyed was duly and properly made;

(b) instrument of transfer so destroyed was duly registered;

(c) share certificate so destroyed was duly cancelled; and

(d) other document so destroyed had been properly dealt with under its terms and was valid and effective according to the particulars in the records of the Company.

42.3 This Article shall only apply to the destruction of a document in good faith and without notice of any claim (regardless of the parties to it) to which the document might be relevant. Nothing in this Article shall be construed as imposing any liability on the Company in respect of the destruction of any such document other than as provided for in this Article which would not attach to the Company in the absence of this Article. References in this Article to the destruction of any document include references to the disposal of it in any manner.

42.4 References in this Article to instruments of transfer shall include, in relation to uncertificated shares, instructions and/or notifications made in accordance with the relevant system relating to the transfer of such shares.

43 Sub-Division

Any resolution authorising the Company to sub-divide its shares or any of them may determine that, as between the shares resulting from the sub-division, any of them may have any preference or advantage or be subject to any restriction as compared with the others.

44 Fractions

If any shares are consolidated or consolidated and then divided, the Board has power to deal with any fractions of shares which result. If the Board decides to sell any shares representing fractions, it can do so for the best price reasonably obtainable and distribute the net proceeds of sale among members in proportion to their fractional entitlements. The Board can arrange for any shares representing fractions to be entered in the Register as certificated shares if they consider that this makes it easier to sell them. The Board can sell those shares to anyone, including the Company if the legislation allows, and may authorise any person to transfer or deliver the shares to the buyer or in accordance with the buyer's instructions. The buyer shall not be bound to see to the application of the purchase money, nor shall his title to the share be affected by any irregularity or invalidity in the proceedings in reference to the sale.

45 Annual General Meetings

An annual general meeting shall be held once a year, at such time (consistent with the terms of the Companies Acts) and place as may be determined by the Board.

46 Convening of General Meetings

All meetings other than annual general meetings shall be called general meetings. The Board may, whenever it thinks fit, and shall on requisition in accordance with the Companies Acts, proceed to convene a general meeting.

47 **Notice of General Meetings**

A general meeting shall be called by at least such minimum notice as is required or permitted by the Companies Acts. The period of notice shall in either case be exclusive of the day on which it is served or deemed to be served and of the day on which the meeting is to be held and shall be given to all members other than those who are not entitled to receive such notices from the Company. The Company may give such notice by any means or combination of means permitted by the Companies Acts.

48 **Contents of Notice of Meetings**

48.1 Every notice calling a meeting shall specify the place, date and time of the meeting, and there shall appear with reasonable prominence in every such notice a statement that a member entitled to attend and vote is entitled to a proxy or (if he has more than one share) proxies to exercise all or any of his rights to attend, speak and vote and that a proxy need not be a member of the Company. Such notice shall also include the address of the website on which the information required by the Act is published, state the procedures with which members must comply in order to be able to attend and vote at the meeting (including the date by which they must comply), provide details of any forms to be used for the appointment of a proxy and state that a member has the right to ask questions at the meeting in accordance with the Act.

48.2 The notice shall specify the general nature of the business to be transacted at the meeting and shall set out the text of all resolutions to be considered by the meeting and shall state in each case whether it is proposed as an ordinary resolution or as a special resolution.

48.3 In the case of an annual general meeting, the notice shall also specify the meeting as such.

48.4 For the purposes of determining which persons are entitled to attend or vote at a meeting and how many votes a person may cast, the Company may specify in the notice of meeting a time, not more than 48 hours before the time fixed for the meeting (not taking into account non-working days) by which a person must be entered in the Register in order to have the right to attend or vote at the meeting or appoint a proxy to do so.

49 **Omission to Give Notice and Non-Receipt of Notice**

The accidental omission to give notice of any meeting or to send an instrument of proxy (where this is intended to be sent out with the notice) to or the non-receipt of either by, any person entitled to receive the same shall not invalidate the proceedings of that meeting.

50 **Postponement of General Meeting**

If the Board considers that it is impracticable or unreasonable to hold a general meeting on the date or at the time or place stated in the notice calling the meeting, it may postpone or move the meeting (or do both). The Board shall take reasonable steps to ensure that notice of the date, time and place of the rearranged meeting is given to any member trying to attend the meeting at the original time and place. Notice of the date, time and place of the rearranged meeting shall, if practicable, also be placed in at least two national newspapers published in the United Kingdom. Notice of the business to be transacted at such rearranged meeting shall not be required. If a meeting is rearranged in this way, appointments of proxy are valid if they are received as required by these Articles not less than 48 hours before the time appointed for holding the rearranged meeting and for the purpose of calculating this period, the Board can decide in their absolute discretion, not to take account of any part of a day that is not a working day. The Board may also postpone or move the rearranged meeting (or do both) under this Article.

51 **Quorum at General Meeting**

No business shall be transacted at any general meeting unless a quorum is present. If a quorum is not present a chairman of the meeting can still be chosen and this will not be treated as part of the business of the meeting. Two members present in person or by proxy and entitled to attend and to vote on the business to be transacted shall be a quorum.

52 **Procedure if Quorum Not Present**

If a quorum is not present within 15 minutes (or such longer interval as the chairman in his absolute discretion thinks fit) from the time appointed for holding a general meeting, or if a quorum ceases to be present during a meeting, the meeting shall be dissolved if convened on the requisition of members. In any other case, the meeting shall stand adjourned to another day, (not being less than ten clear days after the date of the original meeting), and at such time and place as the chairman (or, in default, the Board) may determine. If at such adjourned meeting a quorum is not present within 15 minutes from the time appointed for holding the meeting, one person entitled to vote on the business to be transacted, being a member or a proxy for a member or a duly authorised representative of a corporation which is a member, shall be a quorum and any notice of an adjourned meeting shall state this.

53 **Chairman of General Meeting**

53.1 The chairman of the Board shall preside at every general meeting of the Company. If there is no such chairman or if at any meeting he shall not be present within five minutes after the time appointed for holding the meeting, or shall be unwilling to act as chairman, the deputy chairman (if any) of the Board shall, if present and willing to act, preside at such meeting. If more than one deputy chairman is present they shall agree amongst themselves who is to take the chair or, if they cannot agree, the deputy chairman who has been in office as a director the longest shall take the chair.

53.2 If no chairman or deputy chairman shall be so present and willing to act, the Directors present shall choose one of their number to act or, if there be only one Director present, he shall be chairman if willing to act. If there be no Director present and willing to act, the members present and entitled to vote shall choose one of their number to be chairman of the meeting. Nothing in these Articles shall restrict or exclude any of the powers or rights of a chairman of a meeting which are given by law.

54 **Entitlement to Attend and Speak**

A Director (and any other person invited by the chairman to do so) may attend and speak at any general meeting and at any separate meeting of the holders of any class of shares of the Company, whether or not he is a member.

55 **Adjournments**

The chairman may, with the consent of a meeting at which a quorum is present, and shall, if so directed by the meeting, adjourn any meeting from time to time (or indefinitely) and from place to place as the meeting shall determine. However, without prejudice to any other power which he may have under these Articles or at common law, the chairman may, without the need for the consent of the meeting, interrupt or adjourn any meeting from time to time and from place to place or for an indefinite period if he is of the opinion that it has become necessary to do so in order to secure the proper and orderly conduct of the meeting or to give all persons entitled to do so a reasonable opportunity of attending, speaking and voting at the meeting or to ensure that the business of the meeting is properly disposed of.

56 **Notice of Adjournment**

If the meeting is adjourned indefinitely or for more than three months, notice of the adjourned meeting shall be given in the same manner as in the case of the original meeting. Except as provided in these Articles, there is no need to give notice of the adjourned meeting or of the business to be considered there.

57 **Business of Adjourned Meeting**

No business shall be transacted at any adjourned meeting other than the business which might properly have been transacted at the meeting from which the adjournment took place.

58 **Security Arrangement and Orderly Conduct**

58.1 The Board may direct that any person wishing to attend any meeting should provide such evidence of identity and submit to such searches or other security arrangements or restrictions as the Board shall consider appropriate in the circumstances and shall be entitled in its absolute discretion to refuse entry to any meeting to any person who fails to provide such evidence of identity or to submit to such searches or to otherwise comply with such security arrangements or restrictions.

58.2 The chairman shall take such action or give directions as he thinks fit to promote the orderly conduct of the business of the meeting as laid down in the notice of the meeting and to ensure the security of the meeting and the safety of the people attending the meeting. The chairman's decision on matters of procedure or arising incidentally from the business of the meeting shall be final as shall be his determination as to whether any matter is of such a nature.

59 **Overflow Meeting Rooms**

59.1 The Board may, in accordance with this Article, make arrangements for members and proxies who are entitled to attend and participate in a general meeting, but who cannot be seated in the main meeting room where the chairman will be, to attend and take part in a general meeting in an overflow room or rooms. Any overflow room will have appropriate links to the main room and will enable audio-visual communication between the meeting rooms throughout the meeting. The Board will decide how to divide members and proxies between the main room and the overflow room. If an overflow room is used, the meeting will be treated as being held and taking place in the main meeting room and the meeting will consist of all the members and proxies who are attending both in the main meeting room and the overflow room.

59.2 Details of any arrangements for overflow rooms will be set out in the notice of the meeting but failure to do so will not invalidate the meeting.

60 **Satellite Meeting Places**

60.1 To facilitate the organisation and administration of any general meeting, the Board may decide that the meeting shall be held at two or more locations.

60.2 For the purposes of these Articles, any general meeting of the Company taking place at two or more locations shall be treated as taking place where the chairman of the meeting presides (the **principal meeting place**) and any other location where that meeting takes place is referred in these Articles as a **satellite meeting**.

60.3 A member present in person or by proxy at a satellite meeting may be counted in the quorum and may exercise all rights that they would have been able to exercise if they were present at the principal meeting place.

60.4 The Board may make and change from time to time such arrangements as they shall in their absolute discretion consider appropriate to:

(a) ensure that all members and proxies for members wishing to attend the meeting can do so;

(b) ensure that all persons attending the meeting are able to participate in the business of the meeting and to see and hear anyone else addressing the meeting;

(c) ensure the safety of persons attending the meeting and the orderly conduct of the meeting; and

(d) restrict the numbers of members and proxies at any one location to such number as can safely and conveniently be accommodated there.

60.5 The entitlement of any member or proxy to attend a satellite meeting shall be subject to any such arrangements then in force and stated by the notice of the meeting or adjourned meeting to apply to the meeting.

60.6 If there is a failure of communication equipment or any other failure in the arrangements for participation in the meeting at more than one place, the chairman may adjourn the meeting in accordance with Article 55. Such adjournment will not affect the validity of such meeting, or any business conducted at such meeting up to the point of adjournment, or any action taken pursuant to such meeting.

60.7 A person (**satellite chairman**) appointed by the Board shall preside at each satellite meeting. Every satellite chairman shall carry out all requests made of him by the chairman of the meeting, may take such action as he thinks necessary to maintain the proper and orderly conduct of the satellite meeting and shall have all powers necessary or desirable for such purposes.

61 **Amendment to Resolutions**

61.1 If an amendment to any resolution under consideration is proposed but is ruled out of order by the chairman of the meeting in good faith, any error in such ruling shall not invalidate the proceedings on the original resolution.

61.2 In the case of a resolution duly proposed as a special resolution, no amendment to it (other than an amendment to correct a patent error) may in any event be considered or voted on. In the case of a resolution duly proposed as an ordinary resolution no amendment to it (other than an amendment to correct a patent error) may be considered or voted on unless either at least 48 hours prior to the time appointed for holding the meeting or adjourned meeting at which such ordinary resolution is to be proposed, notice in writing of the terms of the amendment and intention to move the same has been lodged at the Office or received in electronic form at the electronic address at which the Company has or is deemed to have agreed to receive it or the chairman of the meeting in his absolute discretion decides that it may be considered or voted on.

62 **Members' Resolutions**

62.1 Members of the Company shall have the rights provided by the Companies Acts to have the Company circulate and give notice of a resolution which may be properly moved, and is intended to be moved, at the Company's next annual general meeting.

62.2 Expenses of complying with these rights shall be borne in accordance with the Companies Acts.

63 **Method of Voting**

63.1 At any general meeting a resolution put to a vote of the meeting shall be decided on a show of hands, unless (before or on the declaration of the result of the show of hands) a poll is duly demanded. Subject to the Companies Acts, a poll may be demanded by:

(a) the chairman of the meeting; or

(b) at least two members present in person (or by proxy) and entitled to vote at the meeting; or

(c) a member or members present in person (or by proxy) representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting; or

(d) a member or members present in person (or by proxy) holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

63.2 The chairman of the meeting may also demand a poll before a resolution is put to the vote on a show of hands.

63.3 At general meetings, resolutions shall be put to the vote by the chairman of the meeting and there shall be no requirement for the resolution to be proposed or seconded by any person.

63.4 Unless a poll is duly demanded and the demand is not withdrawn, a declaration by the chairman of the meeting that a resolution has on a show of hands been carried, or carried unanimously or by a particular majority, or lost, or not carried by a particular majority, and an entry to that effect in the book containing the minutes of proceedings of the Company, shall be conclusive evidence of the fact, without proof of the number or proportion of the votes recorded in favour of or against such resolution.

64 **Objection to Error in Voting**

No objection shall be raised to the qualification of any voter or to the counting of, or failure to count, any vote, except at the meeting or adjourned meeting at which the vote objected to is given or tendered or at which the error occurs. Any objection or error shall be referred to the chairman of the meeting and shall only vitiate the decision of the meeting on any resolution if the chairman decides that the same is of sufficient magnitude to vitiate the resolution or may otherwise have affected the decision of the meeting. The decision of the chairman of the meeting on such matters shall be final and conclusive.

65 **Procedure on a Poll**

65.1 Any poll duly demanded on the election of a chairman or on any question of adjournment shall be taken immediately. A poll duly demanded on any other matter shall be taken in such manner (including the use of ballot or voting papers or tickets) and at such time and place, not more than 30 days from the date of the meeting or adjourned meeting at which the poll was demanded, as the chairman shall direct. The chairman may appoint scrutineers who need not be members. It is not necessary to give notice of a poll not taken immediately if the time and place at which it is to be taken are announced at the meeting at which it is demanded. In any other case, at least seven clear days' notice shall be given specifying the time, date and place at which the poll shall be taken. The result of the poll shall be deemed to be the resolution of the meeting at which the poll was demanded.

65.2 The demand for a poll (other than on the election of a chairman or any question of adjournment) shall not prevent the continuance of the meeting for the transaction of any business other than the question on which a poll has been demanded.

65.3 The demand for a poll may, before the poll is taken, be withdrawn, but only with the consent of the chairman of the meeting. A demand so withdrawn validates the result of a show of hands declared before the demand was made. If a poll is demanded before the declaration of the result of a show of hands and the demand is duly withdrawn, the meeting shall continue as if the demand had not been made.

65.4 On a poll votes may be given in person or by proxy. A member entitled to more than one vote need not, if he votes, use all his votes or cast all the votes he uses in the same way.

66 **Votes of Members**

66.1 Subject to Article 66.2, the Companies Acts, to any special terms as to voting on which any shares may have been issued or may for the time being be held and to any suspension or abrogation of voting rights under these Articles, at any general meeting every member who is present in person (or by proxy) shall on a show of hands have one vote and every member present in person (or by proxy) shall on a poll have one vote for each share of which he is the holder.

66.2 On a show of hands, a duly appointed proxy has one vote for and one vote against a resolution if the proxy has been appointed by more than one member entitled to vote on the resolution and the proxy has been instructed:

(a) by one or more of those members to vote for the resolution and by one or more other of those members to vote against it; or

(b) by one or more of those members to vote either for or against the resolution and by one or more other of those members to use his/her discretion as to how to vote.

66.3 If two or more persons are joint holders of a share, then in voting on any question the vote of the senior who tenders a vote, whether in person or by proxy, shall be accepted to the exclusion of the votes of the other joint holders. For this purpose seniority shall be determined by the order in which the names of the holders stand in the Register.

66.4 Where in England or elsewhere a receiver or other person (by whatever name called) has been appointed by any court claiming jurisdiction in that behalf to exercise powers with respect to the property or affairs of any member on the ground (however formulated) of mental disorder, the Board may in its absolute discretion, upon or subject to production of such evidence of the appointment as the Board may require, permit such receiver or other person on behalf of such member to vote in person, on a show of hands or on a poll, by proxy on behalf of such member at any general meeting or to exercise any other right conferred by membership in relation to meetings of the Company. Evidence to the satisfaction of the Board of the authority of the person claiming to exercise the right to vote shall be deposited at the Office, or at such other place as is specified in accordance with these Articles for the deposit of instruments of proxy, at least 48 hours before the time appointed for holding the meeting or adjourned meeting at which the right to vote is to be exercised and, in default, the right to vote shall not be exercisable.

66.5 In the case of equality of votes whether on a show of hands or on a poll, the chairman of the meeting at which the show of hands takes place or at which the poll is demanded shall not be entitled to a casting vote.

67 **No Right to Vote Where Sums Overdue on Shares**

No member may vote at a general meeting (or any separate meeting of the holders of any class of shares), either in person or by proxy, or to exercise any other right or privilege as a member in respect of a share held by him unless:

(a) all calls or other sums presently due and payable by him in respect of that share whether alone or jointly with any other person together with interest and expenses (if any) have been paid to the Company; or

(b) the Board determines otherwise.

68 **Voting by Proxy**

68.1 Subject to Article 68.2, an instrument appointing a proxy shall be in writing in any usual form (or in another form approved by the Board) executed under the hand of the appointer or his duly constituted attorney or, if the appointer is a corporation, under its seal or signed by a duly authorised officer or attorney or other person authorised to sign.

68.2 Subject to the Companies Acts, the Board may accept the appointment of a proxy received by electronic means on such terms and subject to such conditions as it considers fit. The appointment of a proxy received by electronic means shall not be subject to the requirements of Article 68.1.

68.3 For the purposes of Articles 68.1 and 68.2, the Board may require such reasonable evidence it considers necessary to determine:

(a) the identity of the member and the proxy; and

(b) where the proxy is appointed by a person acting on behalf of the member, the authority of that person to make the appointment.

68.4 A member may appoint another person as his proxy to exercise all or any of his rights to attend and to speak and to vote (both on a show of hands and on a poll) on a resolution or amendment of a resolution, or on other business arising, at a meeting or meetings of the Company. Unless the contrary is stated in it, the appointment of a proxy shall be deemed to confer authority to exercise all such rights, as the proxy thinks fit.

68.5 A proxy need not be a member.

68.6 A member may appoint more than one proxy in relation to a meeting, provided that each proxy is appointed to exercise the rights attached to different shares held by the member. When two or more valid but differing appointments of proxy are delivered or received for the same share for use at the same meeting, the one which is last validly delivered or received (regardless of its date or the date of its execution) shall be treated as replacing and revoking the other or others as regards that share. If the Company is unable to determine which appointment was last validly delivered or received, none of them shall be treated as valid in respect of that share.

68.7 Delivery or receipt of an appointment of proxy does not prevent a member attending and voting in person at the meeting or an adjournment of the meeting or on a poll.

68.8 The appointment of a proxy shall (unless the contrary is stated in it) be valid for an adjournment of the meeting as well as for the meeting or meetings to which it relates. The appointment of a proxy shall be valid for 12 months from the date of execution or, in the case of an appointment of proxy delivered by electronic means, for 12 months from the date of delivery unless otherwise specified by the Board.

68.9 Subject to the Companies Acts, the Company may send a form of appointment of proxy to all or none of the persons entitled to receive notice of and to vote at a meeting. If sent, the form shall provide for three-way voting on all resolutions (other than procedural resolutions) set out in the notice of meeting.

69 **Receipt of Proxy**

69.1 An instrument appointing a proxy and any reasonable evidence required by the Board in accordance with Article 68.3 shall:

(a) subject to Articles 69.1(c) and (d), in the case of an instrument of proxy in hard copy form, delivered to the office, or another place in the United Kingdom specified in the notice convening the meeting or in the form of appointment of proxy or other accompanying document sent by the Company in relation to the meeting (a **proxy notification address**) not less than 48 hours before the time for holding the meeting or adjourned meeting at which the person named in the form of appointment of proxy proposes to vote;

(b) subject to Articles 69.1(c) and (d), in the case of an appointment of a proxy sent by electronic means, where the Company has given an electronic address (a proxy notification electronic address):

(i) in the notice calling the meeting;

(ii) in an instrument of proxy sent out by the Company in relation to the meeting;

(iii) in an invitation to appoint a proxy issued by the Company in relation to the meeting; or

(iv) on a website maintained by or on behalf of the Company on which any information relating to the meeting is required by the Act to be kept,

it shall be received at such proxy notification electronic address not less than 48 hours before the time for holding the meeting or adjourned meeting at which the person named in the form of appointment of proxy proposes to vote;

(c) in the case of a poll taken more than 48 hours after it is demanded, delivered or received at a proxy notification address or a proxy notification electronic address and not less than 24 hours before the time appointed for the holding of the adjourned meeting or the taking of the poll; or

(d) in the case of a poll which is not taken at the meeting at which it is demanded but is taken 48 hours or less after it is demanded, or in the case of an adjourned meeting to be held 48 hours or less after the time fixed for holding the original meeting, received:

(i) at a proxy notification address or a proxy notification electronic address in accordance with Articles 69.1(a) or (b);

(ii) by the chairman of the meeting or the secretary or any director at the meeting at which the poll is demanded or, as the case may be, at the original meeting; or

(iii) at a proxy notification address or a proxy notification electronic address by such time as the chairman of the meeting may direct at the meeting at which the poll is demanded.

In calculating the periods in this Article, no account shall be taken of any part of a day that is not a working day.

69.2 The Board may decide, either generally or in any particular case, to treat a proxy appointment as valid notwithstanding that the appointment or any of the information required under Article 68.3 has not been received in accordance with the requirements of this Article.

69.3 Subject to Article 69.2, if the proxy appointment and any of the information required under Article 68.3 is not received in the manner set out in Article 69.1, the appointee shall not be entitled to vote in respect of the shares in question.

69.4 Without limiting the foregoing, in relation to any uncertificated shares, the Board may from time to time:

(a) permit appointments of a proxy by means of a communication sent in electronic form in the form of an uncertificated proxy instruction; and

(b) permit supplements to, or amendments or revocations of, any such uncertificated proxy instruction by the same means.

The Board may in addition prescribe the method of determining the time at which any such uncertificated proxy instruction is to be treated as received by the Company or a participant acting on its behalf. The Board may treat any such uncertificated proxy instruction which purports to be or is expressed to be sent on behalf of a holder of a share as sufficient evidence of the authority of the person sending that instruction to send it on behalf of that holder.

70 **Revocation of Proxy**

A vote given or poll demanded by a proxy shall be valid in the event of the death or mental disorder of the principal or the revocation of the instrument of proxy, or of the authority under which the instrument of proxy was executed, or the transfer of the share for which the instrument of proxy is given, unless notice in writing of such death, mental disorder, revocation or transfer shall have been received by the Company at the Office, or at such other place as has been appointed for the deposit of instruments of proxy, no later than the last time at which an appointment of a proxy should have been received in order for it to be valid for use at the meeting or on the holding of the poll at which the vote was given or the poll taken.

71 **Corporate Representatives**

71.1 A corporation (whether or not a company within the meaning of the Act) which is a member may, by resolution of its directors or other governing body, authorise such person as it thinks fit to act as its representative (or, as the case may be, representatives) at any meeting of the Company or at any separate meeting of the holders of any class of shares.

71.2 Any person so authorised shall be entitled to exercise the same powers on behalf of the corporation (in respect of that part of the corporation's holdings to which the authority relates) as the corporation could exercise if it were an individual member.

71.3 The corporation shall for the purposes of these Articles be deemed to be present in person and at any such meeting if a person so authorised is present at it, and all references to attendance and voting in person shall be construed accordingly.

71.4 A Director, the Secretary or some person authorised for the purpose by the Secretary may require the representative to produce a certified copy of the resolution so authorising him or such other evidence of his authority reasonably satisfactory to them before permitting him to exercise his powers.

71.5 A vote given or a poll demanded by a corporate representative shall be valid notwithstanding that he is no longer authorised to represent the member unless notice of the revocation of appointment was delivered in writing to the Company at such place or address and by such time as is specified in Article 70 for the revocation of the appointment of a proxy.

72 **Failure to Disclose Interests in Shares**

72.1 If a member, or any other person appearing to be interested in shares held by that member, has been issued with a notice under section 793 of the Act (**section 793 notice**) and has failed in relation to any shares (**default shares,** which expression includes any shares issued after the date of such notice in right of those shares) to give the Company the information required by the section 793 notice within the prescribed period from the service of the notice, the following sanctions shall apply unless the Board determines otherwise:

(a) the member shall not be entitled in respect of the default shares to be present or to vote (either in person or by representative or proxy) at any general meeting or at any separate meeting of the holders of any class of shares or on any poll or to exercise any other right conferred by membership in relation to any such meeting or poll; and

(b) where the default shares represent at least 0.25% in nominal value of the issued shares of their class (calculated exclusive of any shares held as treasury shares):

(i) any dividend or other money payable for such shares shall be withheld by the Company, which shall not have any obligation to pay interest on it, and the member shall not be entitled to elect, pursuant to Article 130, to receive shares instead of that dividend; and

(ii) no transfer, other than an excepted transfer, of any shares held by the member shall be registered unless the member himself is not in default of supplying the required information and the member proves to the satisfaction of the Board that no person in default of supplying such information is interested in any of the shares that are the subject of the transfer.

For the purposes of ensuring Article 72.1(b)(ii) can apply to all shares held by the member, the Company may in accordance with the uncertificated securities rules, issue a written notification to the Operator requiring conversion into certificated form of any share held by the member in uncertificated form.

72.2 Where the sanctions under Article 72.1 apply in relation to any shares, they shall cease to have effect (and any dividends withheld under Article 72.1(b) shall become payable):

(a) if the shares are transferred by means of an excepted transfer but only in respect of the shares transferred; or

(b) at the end of the period of seven days (or such shorter period as the Board may determine) following receipt by the Company of the information required by the section 793 notice and the Board being fully satisfied that such information is full and complete.

72.3 Where, on the basis of information obtained from a member in respect of any share held by him, the Company issues a section 793 notice to any other person, it shall at the same time send a copy of the notice to the member, but the accidental omission to do so, or the non-receipt by the member of the copy, shall not invalidate or otherwise affect the application of Article 72.1.

72.4 For the purposes of this Article:

(a) a person, other than the member holding a share, shall be treated as appearing to be interested in that share if the member has informed the Company that the person is, or may be, so interested, or if the Company (after taking account of any information obtained from the member or, pursuant to a section 793 notice, from anyone else) knows or has reasonable cause to believe that the person is, or may be, so interested;

(b) **interested** shall be construed as it is for the purpose of section 793 of the Act;

(c) reference to a person having failed to give the Company the information required by a notice, or being in default as regards supplying such information, includes reference:

(i) to his having failed or refused to give all of any part of it; and

(ii) to his having given information which he knows to be false in a material particular or having recklessly given information which is false in a material particular;

(d) **prescribed period** means 14 days;

(e) **excepted transfer** means, in relation to any shares held by a member:

(i) a transfer by way of or pursuant to acceptance of a takeover offer for the Company (within the meaning of section 974 of the Act); or

(ii) a transfer in consequence of a sale made through a recognised investment exchange (as defined in section 285 of the FSMA) or any other stock exchange outside the United Kingdom on which the Company's shares are normally traded; or

(iii) a transfer which is shown to the satisfaction of the Board to be made in consequence of a sale of the whole of the beneficial interest in the shares to a person who is unconnected with the member and with any other person appearing to be interested in the shares.

72.5 Nothing contained in this Article shall be taken to limit the powers of the Company under section 794 of the Act.

73 **Power of Sale of Shares of Untraced Members**

73.1 The Company shall be entitled to sell at the best price reasonably obtainable any share of a member, or any share to which a person is entitled by transmission, if and provided that:

(a) during the period of 12 years before the date of sending of the notice referred to in Article 73.1(b) no cheque, order or warrant in respect of such share sent by the Company through the post in a pre-paid envelope addressed to the member or to the person entitled by transmission to the share, at his address on the Register or other last known address given by the member or person to which cheques, orders or warrants in respect of such share are to be sent has been cashed and the Company has received no communications in respect of such share from such member or person entitled, provided that during such period of 12 years the Company has paid at least three cash dividends (whether interim or final) and no such dividend has been claimed by the person entitled to it;

(b) on or after expiry of the said period of 12 years, the Company has given notice of its intention to sell such share by sending a notice to the member or person entitled by transmission to the share at his address on the Register or other last known address given by the member or person entitled by transmission to the share and before sending such a notice to the member or other person entitled by transmission, the Company must have used reasonable efforts to trace the member or other person entitled, engaging, if considered appropriate, a professional asset reunification company or other tracing agent and/or giving notice of its intention to sell the share by advertisement in a national newspaper and in a newspaper circulating in the area of the address of the member or person entitled by transmission to the share shown in the Register;

(c) during the further period of three months following the date of such notice and prior to the exercise of the power of sale the Company has not received any communication in respect of such share from the member or person entitled by transmission; and

(d) the Company has given notice to NASDAQ of its intention to make such sale, if shares of the class concerned, or certificated or uncertificated depositary instruments over such shares, are listed on NASDAQ or dealt in on any other recognised stock exchange on which the shares are listed.

73.2 To give effect to any sale of shares under this Article, the Board may authorise some person to transfer the shares in question and may enter the name of the transferee in respect of the transferred shares in the Register even if no share certificate has been lodged for such shares and may issue a new certificate to the transferee. An instrument of transfer executed by that person shall be as effective as if it had been executed by the holder of or the person entitled by transmission to, the shares. The buyer shall not be bound to see to the application of the purchase monies, nor shall his title to the shares be affected by any irregularity or invalidity in the proceedings in reference to the sale. If the shares are in uncertificated form, in accordance with the uncertificated securities rules, the Board may issue a written notification to the Operator requiring the conversion of the share to certificated form.

73.3 If during the period of 12 years referred to in Article 73.1, or during any period ending on the date when all the requirements of Articles 73.1(a) to 73.1(d) have been satisfied, any additional shares have been issued in respect of those held at the beginning of, or previously so issued during, any such period and all the requirements of Articles 73.1(b) to 73.1(d) have been satisfied in regard to such additional shares, the Company shall also be entitled to sell the additional shares.

74 **Application of Proceeds of Sale of Shares of Untraced Members**

The Company shall account to the member or other person entitled to the share for the net proceeds of a sale under Article 73 by carrying all monies relating to such sale to a separate account. The Company shall be deemed to be a debtor to, and not a trustee for, such member or other person in respect of such monies. Monies carried to such separate account may either be employed in the business of the Company or invested in such investments as the Board may think fit. No interest shall be payable to such member or other person in respect of such monies and the Company does not have to account for any money earned on them.

75 **Number of Directors**

Unless otherwise determined by the Company by ordinary resolution, the number of Directors (other than any alternate Directors) shall be at least two but shall not be subject to any maximum number.

76 **Power of Company to Appoint Directors**

Subject to these Articles and the Companies Acts, the Company may by ordinary resolution appoint a person who is willing to act to be a Director, either to fill a vacancy or as an addition to the existing Board but the total number of Directors shall not exceed any maximum number fixed in accordance with these Articles.

77 **Power of Board to Appoint Directors**

Subject to these Articles, the Board shall have power at any time to appoint any person who is willing to act as a Director, either to fill a vacancy or as an addition to the existing Board but the total number of Directors shall not exceed any maximum number fixed in accordance with these Articles.

78 **Eligibility of New Directors**

78.1 No person, other than a retiring Director (by rotation or otherwise), shall be appointed or re-appointed a Director at any general meeting unless:

(a) he is recommended by the Board; or

(b) at least seven but not more than 42 clear days before the date appointed for the meeting the Company has received notice from a member (other than the person proposed) entitled to vote at the meeting of his intention to propose a resolution for the appointment or re-appointment of that person, stating the particulars which would, if he were so appointed or re-appointed, be required to be included in the Company's register of directors and a notice executed by that person of his willingness to be appointed or re-appointed, is lodged at the Office.

78.2 A Director need not be a member of the Company.

79 **Classes and Retirement of Directors**

79.1 Following the Listing, the Directors shall be divided into three classes designated as "Class I", "Class II" and "Class III", respectively. The Board is authorised to assign members of the Board already in office such classes at the time the classification becomes effective.

79.2 At the first annual general meeting of the Company following the Listing, each Director in Class I shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.3 At the second annual general meeting of the Company following the Listing, each Director in Class II shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.4 At the third annual general meeting of the Company following the Listing, each Director in Class III shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.5 At each succeeding annual general meeting of the Company following the third annual general meeting of the Company after the Listing, Directors shall be elected to serve for a term of three years to succeed the Directors of the class whose terms expire at such annual general meeting.

79.6 Notwithstanding the foregoing provisions, each Director shall serve until their successor is duly elected and qualified or until their earlier death, resignation or removal.

80 **Deemed Re-Appointment**

80.1 A Director who retires at an annual general meeting shall (unless he is removed from office or his office is vacated in accordance with these Articles) retain office until the close of the meeting at which he retires or (if earlier) when a resolution is passed at that meeting not to fill the vacancy or to elect another person in his place or the resolution to re-appoint him is put to the meeting and lost.

80.2 If the Company, at any meeting at which a Director retires in accordance with these Articles does not fill the office vacated by such Director, the retiring Director, if willing to act, shall be deemed to be re-appointed unless at that meeting a resolution is passed not to fill the vacancy or elect another person in his place or unless the resolution to re-appoint him is put to the meeting and lost.

81 **Procedure if Insufficient Directors Appointed**

81.1 If:

(a) at the annual general meeting in any year any resolution or resolutions for the appointment or re-appointment of the persons eligible for appointment or re-appointment as Directors are put to the meeting and lost; and

(b) at the end of that meeting the number of Directors is fewer than any minimum number of Directors required under Article 75,

all retiring Directors who stood for re-appointment at that meeting (**Retiring Directors**) shall be deemed to have been re-appointed as Directors and shall remain in office but the Retiring Directors may only act for the purpose of filling vacancies, convening general meetings of the Company and performing such duties as are essential to maintain the Company as a going concern, and not for any other purpose.

81.2 The Retiring Directors shall convene a general meeting as soon as reasonably practicable following the meeting referred to in Article 81.1 and they shall retire from office at that meeting. If at the end of any meeting convened under this Article the number of Directors is fewer than any minimum number of Directors required under Article 75, the provisions of this Article shall also apply to that meeting.

82 **Removal of Directors**

In addition to any power of removal conferred by the Companies Acts, the Company may by special resolution, or by ordinary resolution of which special notice has been given in accordance with section 312 of the Act, remove a director before the expiry of his period of office (without prejudice to a claim for damages for breach of contract or otherwise) and may (subject to these Articles) by ordinary resolution appoint another person who is willing to act to be a director in his place.

83 **Vacation of Office by Director**

83.1 Without prejudice to the provisions for retirement (by rotation or otherwise) contained in these Articles, the office of a Director shall be vacated if:

(a) he resigns by notice in writing delivered to the Secretary at the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting;

(b) he offers to resign by notice in writing delivered to the Secretary at the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting and the Board resolves to accept such offer;

(c) he is requested to resign by all of the other Directors by notice in writing addressed to him at his address as shown in the register of Directors (without prejudice to any claim for damages which he may have for breach of any contract between him and the Company);

(d) he ceases to be a Director by virtue of any provision of the Companies Acts, is removed from office pursuant to these Articles or the Act or becomes prohibited by law from being a Director;

(e) he becomes bankrupt or makes an arrangement or composition with his creditors generally;

(f) a registered medical practitioner who is treating that person gives a written opinion to the Company stating that person has become physically or mentally incapable of acting as a director and may remain so for more than three months, or he is or has been suffering from mental or physical ill health and the Board resolves that his office be vacated; or

(g) he is absent (whether or not his alternate Director appointed by him attends), without the permission of the Board, from Board meetings for six consecutive months and a notice is served on him personally, or at his residential address provided to the Company under section 165 of the Act signed by all the other Directors stating that he shall cease to be a Director with immediate effect (and such notice may consist of several copies each signed by one or more Directors).

83.2 If the office of a Director is vacated for any reason, he shall cease to be a member of any committee or sub-committee of the Board.

84 **Resolution as to Vacancy Conclusive**

A resolution of the Board declaring a Director to have vacated office under the terms of Article 83 shall be conclusive as to the fact and ground of vacation stated in the resolution.

85 **Appointment of Alternate Directors**

85.1 Each Director may appoint any person (including another Director) to be his alternate and may at his discretion remove an alternate Director so appointed. Any appointment or removal of an alternate Director must be by written notice delivered to the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting or in any other manner approved by the Board. The appointment requires the approval of the Board unless it has been previously approved or the appointee is another Director.

85.2 An alternate Director must provide the particulars, and sign any form for public filing required by the Companies Acts relating to his appointment.

86 **Alternate Directors' Participation in Board Meetings**

86.1 Every alternate Director is (subject to his giving to the Company an address within the United Kingdom at which notices may be served on him (and, if applicable, an address in relation to which electronic communications may be received by him)) entitled to receive notice of all meetings of the Board and all committees of the Board of which his appointor is a member and, in his appointor's absence, to attend and vote at such meetings and to exercise all the powers, rights, duties and authorities of his appointor. Each person acting as an alternate Director shall have a separate vote at Board meetings for each Director for whom he acts as alternate Director in addition to his own vote if he is also a Director, but he shall count as only one for the purpose of determining whether a quorum is present.

86.2 Signature by an alternate Director of any resolution in writing of the Board or a committee of the Board will, unless the notice of his appointment provides otherwise, be as effective as signature by his appointor.

87 **Alternate Directors Responsible for Own Acts**

Each person acting as an alternate Director will be an officer of the Company, will alone be responsible to the Company for his own acts and defaults and will not be deemed to be the agent of the Director appointing him.

88 **Interests of Alternate Director**

An alternate Director is entitled to contract and be interested in and benefit from contracts or arrangements with the Company, to be repaid expenses and to be indemnified to the same extent as if he were a Director. However, he is not entitled to receive from the Company any fees for his services as alternate, except such part (if any) of the fee payable to his appointor as such appointor may by written notice to the Company direct.

89 **Revocation of Alternate Director**

An alternate Director will cease to be an alternate Director:

(a) if his appointor revokes his appointment; or

(b) if he resigns his office by notice in writing to the Company; or

(c) if his appointor ceases for any reason to be a Director, provided that if any Director retires but is re-appointed or deemed to be re-appointed at the same meeting, any valid appointment of an alternate Director which was in force immediately before his retirement shall remain in force; or

(d) if any event happens in relation to him which, if he were a Director otherwise appointed, would cause him to vacate his office.

90 **Directors' Fees**

Each of the Directors may be paid a fee at such rate as may from time to time be determined by the Board. However, the aggregate of all fees payable to the Directors (other than amounts payable under any other provision of these Articles) must not exceed £250,000 a year or such higher amount as may from time to time be decided by ordinary resolution of the Company. Any fees payable under this Article shall be distinct from any salary, remuneration or other amounts payable to a Director under any other provisions of these Articles and shall accrue from day to day.

91 **Expenses**

Each Director may be paid his reasonable travelling, hotel and other expenses properly incurred by him in or about the performance of his duties as Director, including any expenses incurred in attending meetings of the Board or any committee of the Board or general meetings or separate meetings of the holders of any class of shares or debentures of the Company. Subject to the Act, the Directors shall have the power to make arrangements to provide a Director with funds to meet expenditure incurred or to be incurred by him for the purposes of the Company or for the purpose of enabling him to perform his duties as an officer of the Company or to enable him to avoid incurring any such expenditure.

92 **Additional Remuneration**

If by arrangement with the Board any Director shall perform or render any special duties or services outside his ordinary duties as a Director and not in his capacity as a holder of employment or executive office, he may be paid such reasonable additional remuneration (whether by way of salary, commission, participation in profits or otherwise) as the Board may determine.

93 **Remuneration of Executive Directors**

The salary or remuneration of any Director appointed to hold any employment or executive office in accordance with these Articles may be either a fixed sum of money, or may altogether or in part be governed by business done or profits made or otherwise determined by the Board, and may be in addition to or instead of any fee payable to him for his services as Director under these Articles.

94 **Pensions and Other Benefits**

94.1 The Board may exercise all the powers of the Company to provide pensions or other retirement or superannuation benefits and to provide death or disability benefits or other allowances or gratuities (whether by insurance or otherwise) for any person who is or has at any time been a Director or employee of:

(a) the Company;

(b) any company which is or was a holding company or a subsidiary undertaking of the Company;

(c) any company which is or was allied to or associated with the Company or a subsidiary undertaking or holding company of the Company; or

(d) a predecessor in business of the Company or of any holding company or subsidiary undertaking of the Company,

and, in each case, for any member of his family (including a spouse or former spouse) and any person who is or was dependent on him.

94.2 The Board may establish, maintain, subscribe and contribute to any scheme, institution, association, club, trust or fund and pay premiums and, subject to the Companies Acts, lend money or make payments to, guarantee or give an indemnity in respect of, or give any financial or other assistance in connection with any of the matters set out in Article 94.1 above. The Board may procure any of such matters to be done by the Company either alone or in conjunction with any other person. Any Director or former Director shall be entitled to receive and retain for his own benefit any pension or other benefit provided under this Article and shall not have to account for it to the Company. The receipt of any such benefit will not disqualify any person from being or becoming a Director of the Company.

95 **Powers of the Board**

95.1 Subject to the Companies Acts, these Articles and to any directions given by special resolution of the Company, the business of the Company will be managed by the Board, which may exercise all the powers of the Company, whether relating to the management of the business or not.

95.2 No alteration of these Articles and no such direction given by the Company shall invalidate any prior act of the Board which would have been valid if such alteration had not been made or such direction had not been given. Provisions contained elsewhere in these Articles as to any specific power of the Board shall not be deemed to limit the general powers given by this Article.

96 **Powers of Directors if Less Than Minimum Number**

If the number of Directors is less than the minimum prescribed in Article 75 or decided by the Company by ordinary resolution, the remaining Director or Directors may act only for the purposes of appointing an additional Director or Directors to make up that minimum or convening a general meeting of the Company for the purpose of making such appointment. If no Director or Directors is or are able or willing to act, two members may convene a general meeting for the purpose of appointing Directors. An additional Director appointed in this way holds office (subject to these Articles) only until the dissolution of the next annual general meeting after his appointment unless he is reappointed during the annual general meeting.

97 **Powers of Executive Directors**

The Board or any committee authorised by the Board may:

(a) delegate or entrust to and confer on any Director holding executive office (including a chief executive or managing director, if appointed) such of its powers, authorities and discretions (with power to sub-delegate) for such time, on such terms and subject to such conditions as it thinks fit; and

(b) revoke, withdraw, alter or vary all or any of such powers.

98 **Delegation to Committees**

98.1 The Board may delegate any of its powers, authorities and discretions (with power to sub-delegate) for such time on such terms and subject to such conditions as it thinks fit to any committee consisting of one or more Directors and (if thought fit) one or more other persons provided that:

(a) a majority of the members of a committee shall be Directors; and

(b) no resolution of a committee shall be effective unless a majority of those present when it is passed are Directors or alternate Directors.

98.2 The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary any such powers and discharge any such committee in whole or in part. Insofar as any power, authority or discretion is so delegated, any reference in these Articles to the exercise by the Board of such power, authority or discretion shall be construed as if it were a reference to the exercise of such power, authority or discretion by such committee.

99 **Local Management**

99.1 The Board may establish any local or divisional boards or agencies for managing any of the affairs of the Company in any specified locality, either in the United Kingdom or elsewhere, and appoint any persons to be members of such local or divisional board, or any managers or agents, and may fix their remuneration.

99.2 The Board may delegate to any local or divisional board, manager or agent so appointed any of its powers, authorities and discretions (with power to sub-delegate) and may authorise the members of any such local or divisional board, or any of them, to fill any vacancies and to act notwithstanding vacancies. Any such appointment or delegation under this Article may be made, on such terms conditions as the Board may think fit. The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary all or any of such powers.

99.3 Subject to any terms and conditions expressly imposed by the Board, the proceedings of any local or divisional board or agency with two or more members shall be governed by such of these Articles as regulate the proceedings of the Board, so far as they are capable of applying.

100 **Board Meetings**

100.1 The Board can decide when and where to have meetings and how they will be conducted. They may also adjourn meetings.

100.2 A Board meeting can be called by any Director. The Secretary must call a Board meeting if asked to do so by a Director.

101 **Notice of Board Meetings**

101.1 Notice of a Board meeting shall be deemed to be duly given to a Director if it is given to him personally or by word of mouth or given in writing or by electronic means to him at his last known address or any other address given by him to the Company for that purpose.

101.2 A Director may waive the requirement that notice be given to him of any Board meeting, either prospectively or retrospectively and any retrospective waiver shall not affect the validity of the meeting or of any business conducted at the meeting.

101.3 It shall not be necessary to give notice of a Board meeting to a Director who is absent from the United Kingdom unless he has asked the Board in writing that notices of Board meetings shall during his absence be given to him at any address in the United Kingdom notified to the Company for this purpose, but he shall not, in such event, be entitled to a longer period of notice than if he had been present in the United Kingdom at that address.

102 **Quorum**

102.1 The quorum necessary for the transaction of business may be determined by the Board (but shall be no less than two persons) and until otherwise determined shall be two persons, each being a Director or an alternate Director. A duly convened meeting of the Board at which a quorum is present shall be competent to exercise all or any of the authorities, powers, and discretions for the time being vested in or exercisable by the Board.

102.2 If a Director ceases to be a director at a Board meeting, he can continue to be present and to act as a director and be counted in the quorum until the end of the meeting if no other Director objects and if otherwise a quorum of Directors would not be present.

103 **Chairman**

103.1 The Board may appoint one or more of its body as chairman or joint chairman and one or more of its body as deputy chairman of its meetings and may determine the period for which he is or they are to hold office and may at any time remove him or them from office.

103.2 If no such chairman or deputy chairman is elected, or if at any meeting neither a chairman nor a deputy chairman is present within ten minutes of the time appointed for holding the same, the Directors present shall choose one of their number to be chairman of such meeting. In the event two or more joint chairmen or, in the absence of a chairman, two or more deputy chairman being present, the joint chairman or deputy chairman to act as chairman of the meeting shall be decided by those Directors present.

104 **Voting**

Questions arising at any Board meeting shall be determined by a majority of votes. In the case of an equality of votes the chairman of that meeting shall have a second or casting vote (unless he is not entitled to vote on the resolution in question).

105 **Participation by Telephone or Other Form of Communication**

105.1 Any Director or his alternate may validly participate in a meeting of the Board or a committee of the Board through the medium of conference telephone or any other form of communications equipment (whether in use when these Articles are adopted or developed subsequently), provided that all persons participating in the meeting are able to hear and speak to each other throughout such meeting.

105.2 A person so participating by telephone or other communication shall be deemed to be present in person at the meeting and shall be counted in a quorum and entitled to vote. Such a meeting shall be deemed to take place where the largest group of those participating is assembled or, if there is no group which is larger than any other group, where the chairman of the meeting then is.

105.3 A resolution passed at any meeting held in the above manner, and signed by the chairman of the meeting, shall be as valid and effectual as if it had been passed at a meeting of the Board (or committee, as the case may be) duly convened and held.

106 **Resolution in Writing**

106.1 A resolution in writing signed or confirmed electronically by all the Directors for the time being entitled to receive notice of a Board meeting and to vote on the resolution and not being less than a quorum (or by all the members of a committee of the Board for the time being entitled to receive notice of such committee meeting and to vote on the resolution and not being less than a quorum of that committee), shall be as valid and effective for all purposes as a resolution duly passed at a meeting of the Board (or committee, as the case may be).

106.2 Such a resolution may consist of several documents or electronic communications in the same form each signed or authenticated by one or more of the Directors or members of the relevant committee.

107 **Proceedings of Committees**

All committees of the Board shall, in the exercise of the powers delegated to them and in the transaction of business, conform with any mode of proceedings and regulations which the Board may prescribe and subject to this shall be governed by such of these Articles as regulate the proceedings of the Board as are capable of applying.

108 **Minutes of Proceedings**

108.1 The Board shall keep minutes of all shareholder meetings, all Board meetings and meetings of committees of the Board. The minutes must include the names of the Directors present.

108.2 Any such minutes, if purporting to be signed by the chairman of the meeting at which the proceedings were held or by the chairman of the next meeting or the Secretary, shall be evidence of the matters stated in such minutes without any further proof.

109 **Validity of Proceedings**

All acts done by a meeting of the Board, or of a committee of the Board, or by any person acting as a Director, alternate Director or member of a committee shall be valid even if it is discovered afterwards that there was some defect in the appointment of any person or persons acting, or that they or any of them were or was disqualified from holding office or not entitled to vote, or had in any way vacated their or his office.

110 **Transactions or Other Arrangements With the Company**

110.1 Subject to the Companies Acts and provided he has declared the nature and extent of his interest in accordance with the requirements of the Companies Acts, a Director who is in any way, whether directly or indirectly, interested in an existing or proposed transaction or arrangement with the Company may:

(a) be a party to, or otherwise interested in, any transaction or arrangement with the Company or in which the Company is otherwise (directly or indirectly) interested;

(b) act by himself or through his firm in a professional capacity for the Company (otherwise than as auditor) and he or his firm shall be entitled to remuneration for professional services as if he were not a Director;

(c) be or become a director or other officer of, or employed by, or a party to a transaction or arrangement with, or otherwise interested in, any body corporate in which the Company is otherwise (directly or indirectly) interested; and

(d) hold any office or place of profit with the Company (except as auditor) in conjunction with his office of Director for such period and upon such terms, including as to remuneration as the Board may decide.

110.2 A Director shall not, save as he may otherwise agree, be accountable to the Company for any benefit which he derives from any such contract, transaction or arrangement or from any such office or employment or from any interest in any such body corporate and no such contract, transaction or arrangement shall be liable to be avoided on the grounds of any such interest or benefit nor shall the receipt of any such remuneration or other benefit constitute a breach of his duty under section 176 of the Act.

111 **Authorisation of Directors' Conflicts of Interest**

111.1 The Board may, in accordance with the requirements set out in this Article, authorise any matter or situation proposed to them by any Director which would, if not authorised, involve a Director (an **Interested Director**) breaching his duty under the Act to avoid conflicts of interest.

111.2 A Director seeking authorisation in respect of a conflict of interest shall declare to the Board the nature and extent of his interest in a conflict of interest as soon as is reasonably practicable. The Director shall provide the Board with such details of the matter as are necessary for the Board to decide how to address the conflict of interest together with such additional information as may be requested by the Board.

111.3 Any authorisation under this Article will be effective only if:

(a) to the extent permitted by the Act, the matter in question shall have been proposed by any Director for consideration in the same way that any other matter may be proposed to the Directors under the provisions of these Articles;

(b) any requirement as to the quorum for consideration of the relevant matter is met without counting the Interested Director and any other interested Director; and

(c) the matter is agreed to without the Interested Director voting or would be agreed to if the Interested Director's and any other interested Director's vote is not counted.

111.4 Any authorisation of a conflict of interest under this Article must be recorded in writing (but the authority shall be effective whether or not the terms are so recorded) and may (whether at the time of giving the authorisation or subsequently):

(a) extend to any actual or potential conflict of interest which may reasonably be expected to arise out of the matter or situation so authorised;

(b) provide that the Interested Director be excluded from the receipt of documents and information and the participation in discussions (whether at meetings of the Directors or otherwise) related to the conflict of interest;

(c) impose upon the Interested Director such other terms for the purposes of dealing with the conflict of interest as the Directors think fit;

(d) provide that, where the Interested Director obtains, or has obtained (through his involvement in the conflict of interest and otherwise than through his position as a Director) information that is confidential to a third party, he will not be obliged to disclose that information to the Company, or to use it in relation to the Company's affairs where to do so would amount to a breach of that confidence; and

(e) permit the Interested Director to absent himself from the discussion of matters relating to the conflict of interest at any meeting of the Directors and be excused from reviewing papers prepared by, or for, the Directors to the extent they relate to such matters.

111.5 Where the Directors authorise a conflict of interest, the Interested Director will be obliged to conduct himself in accordance with any terms and conditions imposed by the Directors in relation to the conflict of interest.

111.6 The Directors may revoke or vary such authorisation at any time, but this will not affect anything done by the Interested Director, prior to such revocation or variation, in accordance with the terms of such authorisation.

111.7 A Director is not required, by reason of being a Director (or because of the fiduciary relationship established by reason of being a director), to account to the Company for any remuneration, profit or other benefit which he derives from or in connection with a relationship involving a conflict of interest which has been authorised by the directors or by the Company in general meeting (subject in each case to any terms, limits or conditions attaching to that authorisation) and no contract shall be liable to be avoided on such grounds.

112 **Directors' Permitted Interests**

112.1 A Director cannot vote or be counted in the quorum on any resolution relating to any transaction or arrangement with the Company in which he has an interest and which may reasonably be regarded as likely to give rise to a conflict of interest but can vote (and be counted in the quorum) on the following:

(a) giving him any security, guarantee or indemnity for any money or any liability which he, or any other person, has lent or obligations he or any other person has undertaken at the request, or for the benefit, of the Company or any of its subsidiary undertakings;

(b) giving any security, guarantee or indemnity to any other person for a debt or obligation which is owed by the Company or any of its subsidiary undertakings, to that other person if the Director has taken responsibility for some or all of that debt or obligation. The Director can take this responsibility by giving a guarantee, indemnity or security;

(c) a proposal or contract relating to an offer of any shares or debentures or other securities for subscription or purchase by the Company or any of its subsidiary undertakings, if the Director takes part because he is a holder of shares, debentures or other securities, or if he takes part in the underwriting or sub-underwriting of the offer;

(d) any arrangement for the benefit of employees of the Company or any of its subsidiary undertakings which only gives him benefits which are also generally given to employees to whom the arrangement relates;

(e) any arrangement involving any other company if the Director (together with any person connected with the Director) has an interest of any kind in that company (including an interest by holding any position in that company or by being a shareholder of that company). This does not apply if he knows that he has a Relevant Interest;

(f) a contract relating to insurance which the Company can buy or renew for the benefit of the Directors or a group of people which includes Directors; and

(g) a contract relating to a pension, superannuation or similar scheme or a retirement, death, disability benefits scheme or employees' share scheme which gives the Director benefits which are also generally given to the employees to whom the scheme relates.

112.2 A Director cannot vote or be counted in the quorum on a resolution relating to his own appointment or the settlement or variation of the terms of his appointment to an office or place of profit with the Company or any other company in which the Company has an interest.

112.3 Where the Directors are considering proposals about the appointment, or the settlement or variation of the terms or the termination of the appointment of two or more Directors to other offices or places of profit with the Company or any company in which the Company has an interest, a separate resolution may be put in relation to each Director and in that case each of the Directors concerned shall be entitled to vote and be counted in the quorum in respect of each resolution unless it concerns his own appointment or the settlement or variation of the terms or the termination of his own appointment or the appointment of another director to an office or place of profit with a company in which the Company has an interest and the Director seeking to vote or be counted in the quorum has a Relevant Interest in it.

112.4 A company shall be deemed to be one in which the Director has a **Relevant Interest** if and so long as (but only if and so long as) he is to his knowledge (either directly or indirectly) the holder of or beneficially interested in one per cent or more of any class of the equity share capital of that company (calculated exclusive of any shares of that class in that company held as treasury shares) or of the voting rights available to members of that company. In relation to an alternate Director, an interest of his appointor shall be treated as an interest of the alternate Director without prejudice to any interest which the alternate Director has otherwise. Where a company in which a Director has Relevant Interest is interested in a contract, he also shall be deemed interested in that contract.

112.5 If a question arises at a Board meeting about whether a Director (other than the chairman of the meeting) has an interest which is likely to give rise to a conflict of interest, or whether he can vote or be counted in the quorum, and the Director does not agree to abstain from voting on the issue or not to be counted in the quorum, the question must be referred to the chairman of the meeting. The chairman's ruling about the relevant Director is final and conclusive, unless the nature and extent of the Director's interests have not been fairly disclosed to the Directors. If the question arises about the chairman of the meeting, the question must be directed to the Directors. The chairman cannot vote on the question but can be counted in the quorum. The Directors' resolution about the chairman is final and conclusive, unless the nature and extent of the chairman's interests have not been fairly disclosed to the Directors.

113 **General**

113.1 For the purposes of Articles 110 to 112 inclusive (which shall apply equally to alternate Directors):

(a) An interest of a person who is connected (which word shall have the meaning given to it by section 252 of the Act) with a Director shall be treated as an interest of the Director.

(b) A contract includes references to any proposed contract and to any transaction or arrangement or proposed transaction or arrangement whether or not consulting a contract.

(c) A conflict of interest includes a conflict of interest and duty and a conflict of duties.

(d) Subject to the Companies Acts, the Company may by ordinary resolution suspend or relax the provisions of Articles 110 to 112 to any extent or ratify any contract not properly authorised by reason of a contravention of any of the provisions of Articles 110 to 112.

114 **Power of Attorney**

The Board may, by power of attorney or otherwise, appoint any person or persons to be the agent or attorney of the Company and may delegate to any such person or persons any of its powers, authorities and discretions (with power to sub-delegate), in each case for such purposes and for such time, on such terms (including as to remuneration) and conditions as it thinks fit. The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary any of such powers.

115 **Exercise of Voting Power**

The Board may exercise or cause to be exercised the voting power conferred by the shares in any other company held or owned by the Company, or any power of appointment to be exercised by the Company, in such manner as it thinks fit (including the exercise of the voting power or power of appointment in favour of the appointment of any Director as a director or other officer or employee of such company or in favour of the payment of remuneration to the directors, officers or employees of such company).

116 **Provision for Employees on Cessation of Business**

The Board may, by resolution, sanction the exercise of the power to make provision for the benefit of persons employed or formerly employed by the Company or any of its subsidiary undertakings, in connection with the cessation or the transfer to any person of the whole or part of the undertaking of the Company or that subsidiary undertaking, but any such resolution shall not be sufficient for payments to or for the benefit of directors, former directors or shadow directors.

117 **Overseas Registers**

Subject to the Companies Acts, the Company may keep an overseas, local or other register and the Board may make and vary such regulations as it thinks fit respecting the keeping of any such register.

118 **Borrowing Powers**

118.1 Subject to these Articles and the Companies Acts, the Board may exercise all the powers of the Company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge all or any part of the undertaking, property and assets (present and future) and uncalled capital of the Company;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the Company or of any third party.

118.2 For the purpose of this Article, **Group** means the Company and its subsidiary undertakings for the time being.

118.3 Borrowings shall be deemed to include the following except in so far as otherwise taken into account:

(a) the nominal amount of any issued and paid up share capital (other than equity share capital) of any subsidiary undertaking of the Company owned otherwise than by a member of the Group;

(b) the nominal amount of any other issued and paid up share capital and the principal amount of any debentures or borrowed moneys which is not at the relevant time beneficially owned by a member of the Group, the redemption or repayment of which is the subject of a guarantee or indemnity by a member of the Group or which any member of the Group may be required to buy;

(c) the principal amount of any debenture (whether secured or unsecured) of a member of the Group beneficially owned otherwise than by a member of the Group;

(d) the outstanding amount raised by acceptances by any bank or accepting house under any acceptance credit opened by or on behalf of any member of the Group; and

(e) the minority proportion of moneys borrowed by a member of the Group and owing to a partly-owned subsidiary undertaking.

118.4 Borrowings shall not include and shall be deemed not to include:

(a) borrowings incurred by any member of the Group for the purpose of repaying within six months of the borrowing the whole or any part (with or without premium) of any borrowings of that or other member of the Group then outstanding, pending their application for such purpose within such period;

(b) the minority proportion of moneys borrowed by a partly owned subsidiary undertaking and not owing to another member of the Group.

118.5 When the aggregate principal amount of borrowings required to be taken into account on any particular date is being ascertained, any particular borrowing then outstanding which is denominated or repayable in a currency other than sterling shall be notionally converted into sterling at the rate of exchange prevailing in London on the last business day before that date or, if it would result in a lower figure, at the rate of exchange prevailing in London on the last business day six months before that date. For these purposes the rate of exchange shall be taken to be the spot rate in London recommended by a London clearing bank, selected by the Board, as being the most appropriate rate for the purchase by the company of the currency in question for sterling on the day in question.

118.6 A certificate or report by the auditors of the Company as to the amount of any borrowings or to the effect that the limit imposed by this Article has not been or will not be exceeded at any particular time or times, shall be conclusive evidence of such amount or fact for the purposes of this Article. Nevertheless the Board may at any time rely on a bona fide estimate of the aggregate of the borrowings. If, in consequence, the limit on borrowings set out in this Article is inadvertently exceeded, the amount of borrowings equal to the excess may be disregarded for 90 days after the date on which by reason of a determination of the auditors of the Company or otherwise the Board becomes aware that such a situation has or may have arisen.

118.7 No person dealing with the Company or any of its subsidiary undertakings shall be concerned to see or enquire whether the said limit is observed and no debt incurred or security given in excess of such limit shall be invalid or ineffectual unless the lender or recipient of the security had, at the time the debt was incurred or security given, express notice that the said limit had been or would be exceeded.

119 **Power to Authenticate Documents**

119.1 Any Director, the Secretary or any person appointed by the Board for the purpose shall have power to authenticate any documents affecting the constitution of the Company and any resolution passed by the Company or the Board or any committee, and any books, records, documents and accounts relating to the business of the Company, and to certify copies or extracts as true copies or extracts. Where any books, records, documents or accounts are not at the Office, the local manager or other officer of the Company who has their custody shall be deemed to be a person appointed by the Board for this purpose. A document purporting to be a copy of a resolution, or an extract from the minutes of a meeting, of the Company or the Board or any committee which is so certified shall be conclusive evidence in favour of all persons dealing with the Company that such resolution has been duly passed or, as the case may be, that any minute so extracted is a true and accurate record of proceedings at a duly constituted meeting.

120 **Use of Seals**

120.1 The Board shall provide for the safe custody of the Seal. A Seal shall not be used without the authority of the Board or of a committee of the Board so authorised.

120.2 Subject as otherwise provided in these Articles, every document which is sealed using the Seal must be signed by at least one authorised person in the presence of a witness who attests the signature. An authorised person for this purpose is any Director, the Secretary or any other person authorised by the Directors for the purpose of signing documents to which the Seal is applied.

120.3 The Seal shall be used only for sealing securities issued by the Company and documents creating or evidencing securities so issued. Any such securities or documents sealed with the Seal shall not require to be signed unless the Board decides otherwise or the law otherwise requires.

120.4 The Board may decide who will sign an instrument to which a Seal is affixed (or in the case of a share certificate, on which the Seal may be printed) either generally or in relation to a particular instrument or type of instrument and may also determine either generally or in a particular case that a signature may be dispensed with or affixed by mechanical means.

121 **Declaration of Dividends**

Subject to the Act and these Articles, the Company may by ordinary resolution declare dividends to be paid to members according to their respective rights and interests in the profits of the Company. However, no dividend shall exceed the amount recommended by the Board.

122 **Interim Dividends**

Subject to the Act, the Board may declare and pay such interim dividends (including any dividend at a fixed rate) as appears to the Board to be justified by the profits of the Company available for distribution. If the Board acts in good faith, it shall not incur any liability to the holders of shares for any loss that they may suffer by the lawful payment of any interim dividend on any other class of shares ranking with or after those shares.

123 **Calculation and Currency of Dividends**

Except as provided otherwise by the rights attached to shares, all dividends:

(a) shall be declared and paid accordingly to the amounts paid up (otherwise than in advance of calls) on the shares on which the dividend is paid;

(b) shall be apportioned and paid proportionately to the amounts paid up on the shares during any portion or portions of the period in respect of which the dividend is paid, but if any share is issued on terms that it shall rank for dividend as from a particular date, it shall rank for dividend accordingly; and

(c) may be declared or paid in any currency. The Board may decide the rate of exchange for any currency conversions that may be required and how any costs involved are to be met.

124 **Amounts Due on Shares can be Deducted from Dividends**

The Board may deduct from any dividend or other money payable to any person on or in respect of a share all such sums as may be due from him to the Company on account of calls or otherwise in relation to the shares of the Company. Sums so deducted can be used to pay amounts owing to the Company in respect of the shares.

125 **Dividends Not in Cash**

The Board may, by ordinary resolution of the Company direct, or in the case of an interim dividend may without the authority of an ordinary resolution direct, that payment of any dividend declared may be satisfied wholly or partly by the distribution of assets, and in particular of paid up shares or debentures of any other company, or in any one or more of such ways. Where any difficulty arises regarding such distribution, the Board may settle it as it thinks fit. In particular, the Board may:

(a) issue fractional certificates (or ignore fractions);

(b) fix the value for distribution of such assets or any part of them and determine that cash payments may be made to any members on the footing of the values so fixed, in order to adjust the rights of members; and

(c) vest any such assets in trustees on trust for the person entitled to the dividend.

126 **No Interest on Dividends**

Unless otherwise provided by the rights attached to the share, no dividend or other monies payable by the Company or in respect of a share shall bear interest as against the Company.

127 **Method of Payment**

127.1 The Company may pay any dividend, interest or other sum payable in respect of a share in cash or by direct debit, bank transfer, cheque, dividend warrant, or money order or by any other method, including by electronic means, as the Board may consider appropriate. For uncertificated shares, any payment may be made by means of the relevant system (subject always to the facilities and requirements of the relevant system) and such payment may be made by the Company or any person on its behalf by sending an instruction to the operator of the relevant system to credit the cash memorandum account of the holder or joint holders of such shares or, if permitted by the Company, of such person as the holder or joint holders may in writing direct.

127.2 The Company may send such payment by post or other delivery service (or by such means offered by the Company as the member or person entitled to it may agree in writing) to the registered address of the member or person entitled to it (or, if two or more persons are holders of the share or are jointly entitled to it because of the death or bankruptcy of the member or otherwise by operation of law, to the registered address of such of those persons as is first named in the Register) or to such person and such address as such member or person may direct in writing.

127.3 Every cheque, warrant, order or other form of payment is sent at the risk of the person entitled to the money represented by it, shall be made payable to the person or persons entitled, or to such other person as the person or persons entitled may direct in writing. Payment of the cheque, warrant, order or other form of payment (including transmission of funds through a bank transfer or other funds transfer system or by such other electronic means as permitted by these Articles or in accordance with the facilities and requirements of the relevant system concerned) shall be good discharge to the Company. If any such cheque, warrant, order or other form of payment has or shall be alleged to have been lost, stolen or destroyed the Company shall not be responsible.

127.4 Any joint holder or other person jointly entitled to a share may give an effective receipt for any dividend or other monies payable in respect of such share.

127.5 The Board may, at its discretion, make provisions to enable any member as the Board shall determine to receive duly declared dividends in a currency or currencies other than sterling. For the purposes of the calculation of the amount receivable in respect of any dividend, the rate of exchange to be used to determine the foreign currency equivalent of any sum payable as a dividend shall be such rate or rates and the payment shall be on such terms and conditions as the Board may in its absolute discretion determine.

128 **Uncashed Dividends**

If cheques, warrants or orders for dividends or other sums payable in respect of a share sent by the Company to the person entitled to them are returned to the Company or left uncashed on two consecutive occasions or, following one occasion, reasonable enquires have failed to establish any new address to be used for the purpose, the Company does not have to send any dividends or other monies payable in respect of that share due to that person until he notifies the Company of an address to be used for the purpose.

129 **Unclaimed Dividends**

All dividends, interest or other sums payable and unclaimed for 12 months after having become payable may be invested or otherwise made use of by the Board for the benefit of the Company until claimed. The Company shall not be a trustee in respect of such unclaimed dividends and will not be liable to pay interest on it. All dividends that remain unclaimed for 12 years after they were first declared or became due for payment shall (if the Board so resolves) be forfeited and shall cease to remain owing by the Company.

130 **Scrip Dividends**

Subject to the Act, the Board may, by ordinary resolution of the Company and subject to such terms and conditions as the Board may determine, offer to any holders of ordinary shares (excluding any member holding shares as treasury shares) the right to elect to receive ordinary shares, credited as fully paid, instead of cash in respect of the whole (or some part, to be determined by the Board) of any dividend specified by the ordinary resolution. The following provisions shall apply:

(a) the said resolution may specify a particular dividend, or may specify all or any dividends declared within a specified period or periods but such period may not end later than the fifth anniversary of the date of the meeting at which the ordinary resolution is passed;

(b) the entitlement of each holder of ordinary shares to new ordinary shares shall be such that the relevant value of the entitlement shall be as nearly as possible equal to (but not greater than) the cash amount (disregarding any tax credit) of the dividend that such holder would have received by way of dividend. For this purpose **relevant value** shall be calculated by reference to the average of the middle market quotations for the ordinary shares, certificated or uncertificated depositary instruments in respect of such shares, on NASDAQ (or any other publication of a recognised investment

exchange showing quotations for the Company's ordinary shares), for the day on which the ordinary shares are first quoted "ex" the relevant dividend and the four subsequent dealing days, or in such other manner as the Board may determine on such basis as it considers to be fair and reasonable. A certificate or report by the Company's auditors as to the amount of the relevant value in respect of any dividend shall be conclusive evidence of that amount;

(c) no fractions of a share shall be allotted. The Board may make such provisions as it thinks fit for any fractional entitlements including provisions where, in whole or in part, the benefit accrues to the Company and/or under which fractional entitlements are accrued and/or retained and in each case accumulated on behalf of any member and such accruals or retentions are applied to the allotment by way of bonus to or cash subscription on behalf of any member of fully paid ordinary shares and/or provisions where cash payments may be made to members in respect of their fractional entitlements;

(d) the Board shall, after determining the basis of allotment, notify the holders of ordinary shares in writing of the right of election offered to them, and specify the procedure to be followed and place at which, and the latest time by which, elections must be lodged in order to be effective. No such notice need to be given to holders of ordinary shares who have previously given election mandates in accordance with this Article and whose mandates have not been revoked. The accidental omission to give notice of any right of election to, or the non-receipt (even if the Company becomes aware of such non-receipt) of any such notice by, any holder of ordinary shares entitled to the same shall neither invalidate any offer of an election nor give rise to any claim, suit or action;

(e) the Board shall not proceed with any election unless the company has sufficient reserves or funds that may be capitalised, and the Board has authority to allot sufficient shares, to give effect to it after the basis of the allotment is determined;

(f) the Board may exclude from any offer or make other arrangements in relation to any holders of ordinary shares where the Board considers that the making of the offer to them or in respect of such shares would or might involve the contravention of the laws of any territory or that for any other reason the offer should not be made to them or in respect of such shares;

(g) the Board may establish or vary a procedure for election mandates in respect of future rights of election and may determine that every duly effected election in respect of any ordinary shares shall be binding on every successor in title to the holder;

(h) the dividend (or that part of the dividend in respect of which a right of election has been offered) shall not be payable on ordinary shares in respect of which an election has been duly made (**elected ordinary shares**) and instead additional ordinary shares shall be allotted to the holders of the elected ordinary shares on the basis of allotment determined as stated above. For such purpose the Board may capitalise, out of any amount for the time being standing to the credit of any reserve or fund (including any share premium account or capital redemption reserve) or of any of the profits which could otherwise have been applied in paying dividends in cash as the Board may determine, a sum equal to the aggregate nominal amount of the additional ordinary shares to be allotted on such basis and apply it in paying up in full the appropriate number of unissued ordinary shares for allotment and distribution to the holders of the elected ordinary shares on such basis. The Board may do all acts and things considered necessary or expedient to give effect to any such capitalisation;

(i) the Board may decide how any costs relating to the new shares available in place of a cash dividend will be met, including to deduct an amount from the entitlement of a holder of ordinary shares under this Article;

(j) the additional ordinary shares so allotted shall rank pari passu in all respects with each other and with the fully paid ordinary shares in issue on the record date for the dividend in respect of which the right of election has been offered, except that they will not rank for any dividend or other distribution or other entitlement which has been declared, paid or made by reference to such record date; and

(k) the Board may terminate, suspend, or amend any offer of the right to elect to receive ordinary shares in lieu of any cash dividend at any time and generally may implement any scrip dividend scheme on such terms and conditions as the Board may determine and take such other action as the Board may deem necessary or desirable in respect of any such scheme.

131 **Capitalisation of Reserves**

131.1 The Board may, with the authority of an ordinary resolution of the Company:

(a) subject as provided in this Article, resolve to capitalise any undivided profits of the Company not required for paying any preferential dividend (whether or not they are available for distribution) or any sum standing to the credit of any reserve or fund of the Company which is available for distribution or standing to the credit of the share premium account of capital redemption reserve or other undistributable reserve;

(b) appropriate the sum resolved to be capitalised to the members in proportion to the nominal amounts of the shares (whether or not fully paid) held by them respectively which would entitle them to participate in a distribution of that sum if the shares were fully paid and the sum were then distributable and were distributed by way of dividend and apply such sum on their behalf either in or towards paying up the amounts, if any, for the time being unpaid on any shares held by them respectively, or in paying up in full unissued shares or debentures of the Company of a nominal amount equal to that sum, and allot the shares or debentures credited as fully paid to those members or as they may direct, in those proportions, or partly in one way and partly in the other, provided that:

(i) the share premium account, the capital redemption reserve, any other undistributable reserve and any profits which are not available for distribution may, for the purposes of this Article, only be applied in paying up in full shares to be allotted to members credited as fully paid;

(ii) the Company will also be entitled to participate in the relevant distribution in relation to any shares of the relevant class held by it as treasury shares and the proportionate entitlement of the relevant class of members to the distribution will be calculated accordingly; and

(iii) in a case where any sum is applied in paying amounts for the time being unpaid on any shares of the Company or in paying up in full debentures of the Company, the amount of the net assets of the Company at that time in not less than the aggregate of the called up share capital of the Company and its undistributable reserves as shown in the latest audited accounts of the Company or such other accounts as may be relevant and would not be reduced below that aggregate by the payment of it;

(c) resolve that any shares so allotted to any member in respect of a holding by him of any partly paid shares shall, so long as such shares remain partly paid, rank for dividends only to the extent that such partly paid shares rank for dividends;

(d) make such provision by the issue of fractional certificates (or by ignoring fractions or by accruing the benefit of it to the Company rather than to the members concerned) or by payment in cash or otherwise as it thinks fit in the case of shares or debentures becoming distributable in fractions;

(e) authorise any person to enter on behalf of such members concerned into an agreement with the Company providing for either:

(i) the allotment to them respectively, credited as fully paid up, of any shares or debentures to which they may be entitled on such capitalisation; or

(ii) the payment up by the Company on behalf of such members by the application of their respective proportions of the reserves or profits resolved to be capitalised, of the amounts or any part of the amounts remaining unpaid on their existing shares,

(any agreement made under such authority being effective and binding on all such members); and

(f) generally do all acts and things required to give effect to such resolution.

132 **Record Dates**

132.1 Notwithstanding any other provision of these Articles but without prejudice to the rights attached to any shares and subject always to the Act, the Company or the Board may by resolution specify any date (**record date**) as the date at the close of business (or such other time as the Board may determine) on which persons registered as the holders of shares or other securities shall be entitled to receipt of any dividend, distribution, interest, allotment, issue, notice, information, document or circular. Such record date may be before, on or after the date on which the dividend, distribution, interest, allotment, issue, notice, information, document or circular is declared, made, paid, given, or served.

132.2 In the absence of a record date being fixed, entitlement to any dividend, distribution, interest, allotment, issue, notice, information, document or circular shall be determined by reference to the date on which the dividend is declared, the distribution allotment or issue is made or the notice, information, document or circular made, given or served.

133 **Inspection of Records**

No member (other than a Director) shall have any right to inspect any accounting record or other document of the Company unless he is authorised to do so by law, by order of a court of competent jurisdiction, by the Board or by ordinary resolution of the Company.

134 **Accounts to be Sent to Members**

134.1 In respect of each financial year, a copy of the Company's annual accounts, the strategic report, the Directors' report, the Directors' remuneration report, the auditor's report on those accounts and on the auditable part of the Directors' remuneration report shall be sent or supplied to:

(a) every member (whether or not entitled to receive notices of general meetings);

(b) every holder of debentures (whether or not entitled to receive notice of general meetings); and

(c) every other person who is entitled to receive notice of general meetings;

not less than 21 clear days before the date of the meeting at which copies of those documents are to be laid in accordance with the Act.

134.2 This Article does not require copies of the documents to which it applies to be sent or supplied to:

(a) a member or holder of debentures of whose address the Company is unaware; or

(b) more than one of the joint holders of shares or debentures.

134.3 The Board may determine that persons entitled to receive a copy of the Company's annual accounts, the strategic report, the Directors' report, the Directors' remuneration report, the auditor's report on those accounts and on the auditable part of the Directors' remuneration report are those persons entered on the Register at the close of business on a day determined by the Board, provided that the day determined by the Board may not be more than 21 days before the day that the relevant copies are being sent.

134.4 Where permitted by the Act, a strategic report with supplementary material in the form and containing the information prescribed by the Act may be sent or supplied to a person so electing in place of the documents required to be sent or supplied by Article 134.1.

135 **Service of Notices**

135.1 The Company can send, deliver or serve any notice or other document, including a share certificate, to or on a member:

(a) personally;

(b) by sending it through the postal system addressed to the member at his registered address or by leaving it at that address addressed to the member;

(c) through a relevant system, where the notice or document relates to uncertificated shares;

(d) where appropriate, by sending or supplying it in electronic form to an address notified by the member to the Company for that purpose;

(e) where appropriate, by making it available on a website and notifying the member of its availability in accordance with this Article; or

(f) by any other means authorised in writing by the member.

135.2 In the case of joint holders of a share:

(a) service, sending or supply of any notice, document or other information on or to one of the joint holders shall for all purposes be deemed a sufficient service on, sending or supplying to all the joint holders; and

(b) anything to be agreed or specified in relation to any notice, document or other information to be served on, sent or supplied to them may be agreed or specified by any one of the joint holders and the agreement or specification of the first named in the Register shall be accepted to the exclusion of that of the other joint holders.

135.3 Where a member (or, in the case of a joint holders, the person first named in the Register) has a registered address outside the United Kingdom but has notified the Company of an address within the United Kingdom at which notices, documents or other information may be given to him or has given to the Company an address for the purposes of communications by electronic means at which notices, documents or other information may be served, sent or supplied to him, he shall be entitled to have notices served, sent or supplied to him at such address or, where applicable, the Company may make them available on a website and notify the holder of that address. Otherwise no such member shall be entitled to receive any notice, document or other information from the Company.

135.4 If on three consecutive occasions any notice, document or other information has been sent to any member at his registered address or his address for the service of notices (by electronic means or otherwise) but has been returned undelivered, such member shall not be entitled to receive notices, documents or other information from the Company until he shall have communicated with the Company and supplied in writing a new registered address or address within the United Kingdom for the service of notices or has informed the Company of an address for the service of notices and the sending or supply of documents and other information in electronic form. For these purposes, any notice, document or other information served, sent or supplied by post shall be treated as returned undelivered if the notice, document or other information is served, sent or supplied back to the Company (or its agents) and a notice, document or other information served, sent or supplied in electronic form shall be treated as returned undelivered if the Company (or its agents) receives notification that the notice, document or other information was not delivered to the address to which it was served, sent or supplied.

135.5 The Company may at any time and in its sole discretion choose to serve, send or supply notices, documents or other information in hard copy form alone to some or all of the members.

136 **Notice on Person Entitled By Transmission**

The Company may give notice to the person entitled to a share because of the death or bankruptcy of a member or otherwise by operation of law, by sending or delivering it in any manner authorised by these Articles for the giving of notice to a member, addressed to that person by name, or by the title of representative of the deceased or trustee of the bankrupt or representative by operation of law or by any like description, at the address (if any) within the United Kingdom supplied for the purpose by the person claimed to be so entitled or to which notices may be sent in electronic form. Until such an address has been so supplied, a notice may be given in any manner in which it might have been given if the death or bankruptcy or operation of law had not occurred.

137 **Record Date for Service**

Any notice, document or other information may be served, sent or supplied by the Company by reference to the register as it stands at any time not more than 15 days before the date of service, sending or supplying. No change in the register after that time shall invalidate that service, sending or supply. Where any notice, document or other information is served on, sent or supplied to any person in respect of a share in accordance with these Articles, no person deriving any title or interest in that share shall be entitled to any further service, sending or supplying of that notice, document or other information.

138 **Evidence of Service**

138.1 Any notice, document or other information, addressed to a member at his registered address or address for service in the United Kingdom shall, if served, sent or supplied by first class post, be deemed to have been served or delivered on the day after the day when it was put in the post (or, where second class post is employed, on the second day after the day when it was put in the post). Proof that an envelope containing the notice, document or other information was properly addressed and put into the post as a prepaid letter shall be conclusive evidence that the notice was given.

138.2 Any notice, document or other information not served, sent or supplied by post but delivered or left at a registered address or address for service in the United Kingdom (other than an address for the purposes of communications by electronic means) shall be deemed to have been served or delivered on the day on which it was so delivered or left.

138.3 Any notice, document or other information, if served, sent or supplied by electronic means shall be deemed to have been received on the day on which the electronic communication was sent by or on behalf of the Company notwithstanding that the Company subsequently

sends a hard copy of such notice, document or other information by post. Any notice, document or other information made available on a website shall be deemed to have been received on the day on which the notice, document or other information was first made available on the website or, if later, when a notice of availability is received or deemed to have been received pursuant to this Article. Proof that the notice, document or other information was properly addressed shall be conclusive evidence that the notice by electronic means was given.

138.4 Any notice, document or other information served, sent or supplied by the Company by means of a relevant system shall be deemed to have been received when the Company or any sponsoring system-participant acting on its behalf sends the issuer-instruction relating to the notice, document or other information.

138.5 Any notice, document or other information served, sent or supplied by the Company by any other means authorised in writing by the member concerned shall be deemed to have been received when the Company has carried out the action it has been authorised to take for that purpose.

139 **Notice When Post not Available**

If at any time by reason of the suspension, interruption or curtailment of postal services within the United Kingdom the Company is unable effectively to convene a general meeting by notices sent through the post, the Company need only give notice of a general meeting to those members with whom the Company can communicate by electronic means and who have provided the Company with an address for this purpose. The Company shall also advertise the notice in at least one national newspaper published in the United Kingdom and make it available on its website from the date of such advertisement until the conclusion of the meeting or any adjournment of it. In any such case the Company shall send confirmatory copies of the notice by post to those members to whom notice cannot be given by electronic means if, at least seven days prior to the meeting, the posting of notices to addresses throughout the United Kingdom again becomes practicable.

140 **Indemnity and Insurance**

140.1 In this Article:

(a) companies are **associated** if one is a subsidiary of the other or both are subsidiaries of the same body corporate;

(b) a **relevant officer** means any Director or other officer or former director or other officer of the Company or an associated company (including any company which is a trustee of an occupational pension scheme (as defined by section 235(6) of the Act), but excluding in each case any person engaged by the Company (or associated company) as auditor (whether or not he is also a director or other officer), to the extent he acts in his capacity as auditor); and

(c) **relevant loss** means any loss or liability which has been or may be incurred by a relevant officer in connection with that relevant officer's duties or powers in relation to the company, any associated company or any pension fund or employees' share scheme of the company or associated company.

140.2 Subject to Article 140.4, but without prejudice to any indemnity to which a relevant officer is otherwise entitled:

(a) each relevant officer shall be indemnified out of the Company's assets against all relevant loss and in relation to the Company's (or any associated company's) activities as trustee of an occupational pension scheme (as defined in section 235(6) of the Act), including any liability incurred by him in defending any civil or criminal proceedings, in which judgment is given in his favour or in which he is acquitted or

the proceedings are otherwise disposed of without any finding or admission of any material breach of duty on his part or in connection with any application in which the court grants him, in his capacity as a relevant officer, relief from liability for negligence, default, breach of duty or breach of trust in relation to the Company's (or any associated company's) affairs; and

(b) the Company may provide any relevant officer with funds to meet expenditure incurred or to be incurred by him in connection with any proceedings or application referred to in Article 140.2(a) and otherwise may take any action to enable any such relevant officer to avoid incurring such expenditure.

140.3 This Article does not authorise any indemnity which would be prohibited or rendered void by any provision of the Companies Acts or by any other provision of law.

140.4 The Directors may decide to purchase and maintain insurance, at the expense of the Company, for the benefit of any relevant officer in respect of any relevant loss.

Exhibit 4.1

DEPOSIT AGREEMENT

by and among

ORCHARD THERAPEUTICS PLC

and

CITIBANK, N.A.,
as Depositary,

and

THE HOLDERS AND BENEFICIAL OWNERS OF
AMERICAN DEPOSITARY SHARES
ISSUED HEREUNDER

Dated as of [●], 2018

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DEPOSIT AGREEMENT

DEPOSIT AGREEMENT, dated as of [●], 2018, by and among (i) Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales, and its successors (the "Company"), (ii) CITIBANK, N.A., a national banking association organized under the laws of the United States of America ("Citibank") acting in its capacity as depositary, and any successor depositary hereunder (Citibank in such capacity, the "Depositary"), and (iii) all Holders and Beneficial Owners of American Depositary Shares issued hereunder (all such capitalized terms as hereinafter defined).

W I T N E S S E T H T H A T:

WHEREAS, the Company desires to establish with the Depositary an ADR facility to provide for the deposit of the Shares (as hereinafter defined) and the creation of American Depositary Shares representing the Shares so deposited and for the execution and Delivery (as hereinafter defined) of American Depositary Receipts (as hereinafter defined) evidencing such American Depositary Shares; and

WHEREAS, the Depositary is willing to act as the Depositary for such ADR facility upon the terms set forth in the Deposit Agreement (as hereinafter defined); and

WHEREAS, any American Depositary Receipts issued pursuant to the terms of the Deposit Agreement are to be substantially in the form of Exhibit A attached hereto, with appropriate insertions, modifications and omissions, as hereinafter provided in the Deposit Agreement; and

WHEREAS, the Board of Directors of the Company (or an authorized committee thereof) has duly approved the establishment of an ADR facility upon the terms set forth in the Deposit Agreement, the execution and delivery of the Deposit Agreement on behalf of the Company, and the actions of the Company and the transactions contemplated herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

ARTICLE I

DEFINITIONS

All capitalized terms used, but not otherwise defined, herein shall have the meanings set forth below, unless otherwise clearly indicated:

Section 1.1 "ADS Record Date" shall have the meaning given to such term in Section 4.9.

Section 1.2 "Affiliate" shall have the meaning assigned to such term by the Commission (as hereinafter defined) under Regulation C promulgated under the Securities Act (as hereinafter defined), or under any successor regulation thereto.

Section 1.3 "**American Depositary Receipt(s)", "ADR(s)" and "Receipt(s)**" shall mean the certificate(s) issued by the Depositary to evidence the American Depositary Shares issued under the terms of the Deposit Agreement in the form of Certificated ADS(s) (as hereinafter defined), as such ADRs may be amended from time to time in accordance with the provisions of the Deposit Agreement. An ADR may evidence any number of ADSs and may, in the case of ADSs held through a central depository such as DTC, be in the form of a "Balance Certificate."

Section 1.4 **"American Depositary Share(s)" and "ADS(s)"** shall mean the rights and interests in the Deposited Property (as hereinafter defined) granted to the Holders and Beneficial Owners pursuant to the terms and conditions of the Deposit Agreement and, if issued as Certificated ADS(s) (as hereinafter defined), the ADR(s) issued to evidence such ADSs. ADS(s) may be issued under the terms of the Deposit Agreement in the form of (a) Certificated ADS(s) (as hereinafter defined), in which case the ADS(s) are evidenced by ADR(s), or (b) Uncertificated ADS(s) (as hereinafter defined), in which case the ADS(s) are not evidenced by ADR(s) but are reflected on the direct registration system maintained by the Depositary for such purposes under the terms of Section 2.13. Unless otherwise specified in the Deposit Agreement or in any ADR, or unless the context otherwise requires, any reference to ADS(s) shall include Certificated ADS(s) and Uncertificated ADS(s), individually or collectively, as the context may require. Each ADS shall represent the right to receive, and to exercise the beneficial ownership interests in, the number of Shares specified in the form of ADR attached hereto as Exhibit A (as amended from time to time) that are on deposit with the Depositary and/or the Custodian, subject, in each case, to the terms and conditions of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS), until there shall occur a distribution upon Deposited Securities referred to in Section 4.2 or a change in Deposited Securities referred to in Section 4.11 with respect to which additional ADSs are not issued, and thereafter each ADS shall represent the right to receive, and to exercise the beneficial ownership interests in, the applicable Deposited Property on deposit with the Depositary and the Custodian determined in accordance with the terms of such Sections, subject, in each case, to the terms and conditions of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS). In addition, the ADS(s)-to-Share(s) ratio is subject to amendment as provided in Article IV of the Deposit Agreement (which may give rise to Depositary fees).

Section 1.5 **"Applicant"** shall have the meaning given to such term in Section 5.10.

Section 1.6 **"Articles of Association"** shall mean the Articles of Association of the Company, as amended and restated from time to time.

Section 1.7 **"Beneficial Owner"** shall mean, as to any ADS, any person or entity having a beneficial interest deriving from the ownership of such ADS. Notwithstanding anything else contained in the Deposit Agreement, any ADR(s) or any other instruments or agreements relating to the ADSs and the corresponding Deposited Property, the Depositary, the Custodian and their respective nominees are intended to be, and shall at all times during the term of the Deposit Agreement be, the record holders only of the Deposited Property represented by the ADSs for the benefit of the Holders and Beneficial Owners of the corresponding ADSs. The Depositary, on its own behalf and on behalf of the Custodian and their respective nominees, disclaims any beneficial ownership interest in the Deposited Property held on behalf of the Holders and Beneficial Owners

of ADSs. The beneficial ownership interests in the Deposited Property are intended to be, and shall at all times during the term of the Deposit Agreement continue to be, vested in the Beneficial Owners of the ADSs representing the Deposited Property. The beneficial ownership interests in the Deposited Property shall, unless otherwise agreed by the Depositary, be exercisable by the Beneficial Owners of the ADSs only through the Holders of such ADSs, by the Holders of the ADSs (on behalf of the applicable Beneficial Owners) only through the Depositary, and by the Depositary (on behalf of the Holders and Beneficial Owners of the corresponding ADSs) directly, or indirectly through the Custodian or their respective nominees, in each case upon the terms of the Deposit Agreement and, if applicable, the terms of the ADR(s) evidencing the ADSs. A Beneficial Owner of ADSs may or may not be the Holder of such ADSs. A Beneficial Owner shall be able to exercise any right or receive any benefit hereunder solely through the person who is the Holder of the ADSs owned by such Beneficial Owner. Unless otherwise identified to the Depositary, a Holder shall be deemed to be the Beneficial Owner of all the ADSs registered in his/her/its name. The manner in which a Beneficial Owner holds ADSs (e.g., in a brokerage account vs. as registered holder) may affect the rights and obligations of, the manner in which, and the extent to which, services are made available to, Beneficial Owners pursuant to the terms of the Deposit Agreement.

Section 1.8 "Certificated ADS(s)" shall have the meaning set forth in Section 2.13.

Section 1.9 "Citibank" shall mean Citibank, N.A., a national banking association organized under the laws of the United States of America, and its successors.

Section 1.10 "Commission" shall mean the Securities and Exchange Commission of the United States or any successor governmental agency thereto in the United States.

Section 1.11 "Company" shall mean Orchard Therapeutics plc, a public limited company incorporated and existing under the laws of England and Wales, and its successors.

Section 1.12 "CREST" shall mean the system for the paperless settlement of trades in securities and the holding of uncertificated securities operated by Euroclear UK & Ireland Limited in accordance with the Uncertificated Securities Regulations 2001 (SI 2001 No. 3755), as amended from time to time, or any successor thereto.

Section 1.13 "Custodian" shall mean (i) as of the date hereof, Citibank, N.A. (London), having its principal office at 25 Canada Square, Canary Wharf, London, E14 5LB, United Kingdom, as the custodian of Deposited Property for the purposes of the Deposit Agreement, (ii) Citibank, N.A., acting as custodian of Deposited Property pursuant to the Deposit Agreement, and (iii) any other entity that may be appointed by the Depositary pursuant to the terms of Section 5.5 as successor, substitute or additional custodian hereunder. The term "Custodian" shall mean any Custodian individually or all Custodians collectively, as the context requires.

Section 1.14 "Deliver" and "Delivery" shall mean (x) *when used in respect of Shares and other Deposited Securities*, whichever is appropriate of (i) the physical delivery of the certificate(s) representing such securities, or (ii) the book-entry transfer and recordation of such securities on the books of the Share Registrar (as hereinafter defined) or in the book-entry

settlement of CREST, and (y) *when used in respect of ADSs*, either (i) the physical delivery of ADR(s) evidencing the ADSs, or (ii) the book-entry transfer and recordation of ADSs on the books of the Depositary or any book-entry settlement system in which the ADSs are settlement-eligible.

Section 1.15 "Deposit Agreement" shall mean this Deposit Agreement and all exhibits hereto, as the same may from time to time be amended and supplemented from time to time in accordance with the terms of the Deposit Agreement.

Section 1.16 "**Depositary**" shall mean Citibank, N.A., a national banking association organized under the laws of the United States, in its capacity as depositary under the terms of the Deposit Agreement, and any successor depositary hereunder.

Section 1.17 "Deposited Property" shall mean the Deposited Securities and any cash and other property held on deposit by the Depositary and the Custodian in respect of the ADSs or the Deposited Securities under the terms of the Deposit Agreement, subject, in the case of cash, to the provisions of Section 4.8. All Deposited Property shall be held by the Custodian, the Depositary and their respective nominees for the benefit of the Holders and Beneficial Owners of the ADSs representing the Deposited Property. The Deposited Property is not intended to, and shall not, constitute proprietary assets of the Depositary, the Custodian or their nominees. Beneficial ownership in the Deposited Property is intended to be, and shall at all times during the term of the Deposit Agreement continue to be, vested in the Beneficial Owners of the ADSs representing the Deposited Property.

Section 1.18 "Deposited Securities" shall mean the Shares and any other securities held on deposit by the Custodian from time to time in respect of the ADSs under the Deposit Agreement and constituting Deposited Property.

Section 1.19 "Dollars" and "$" shall refer to the lawful currency of the United States.

Section 1.20 "DTC" shall mean The Depository Trust Company, a national clearinghouse and the central book-entry settlement system for securities traded in the United States and, as such, the custodian for the securities of DTC Participants (as hereinafter defined) maintained in DTC, and any successor thereto.

Section 1.21 "DTC Participant" shall mean any financial institution (or any nominee of such institution) having one or more participant accounts with DTC for receiving, holding and delivering the securities and cash held in DTC. A DTC Participant may or may not be a Beneficial Owner. If a DTC Participant is not the Beneficial Owner of the ADSs credited to its account at DTC, or of the ADSs in respect of which the DTC Participant is otherwise acting, such DTC Participant shall be deemed, for all purposes hereunder, to have all requisite authority to act on behalf of the Beneficial Owner(s) of the ADSs credited to its account at DTC or in respect of which the DTC Participant is so acting. A DTC Participant, upon acceptance in any one of its DTC accounts of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement, shall (notwithstanding any explicit or implicit disclosure that it may be acting on behalf of another party) be deemed for all purposes to be a party to, and bound by, the terms of the Deposit Agreement and the applicable ADR(s) to the same extent as, and as if the DTC Participant were, the Holder of such ADSs.

Section 1.22 "Exchange Act" shall mean the United States Securities Exchange Act of 1934, as amended from time to time.

Section 1.23 "Foreign Currency" shall mean any currency other than Dollars.

Section 1.24 "Full Entitlement ADR(s)", "Full Entitlement ADS(s)" and "Full Entitlement Share(s)" shall have the respective meanings set forth in Section 2.12.

Section 1.25 "Holder(s)" shall mean the person(s) in whose name the ADSs are registered on the books of the Depositary (or the Registrar, if any) maintained for such purpose. A Holder may or may not be a Beneficial Owner. If a Holder is not the Beneficial Owner of the ADS(s) registered in its name, such person shall be deemed, for all purposes hereunder, to have all requisite authority to act on behalf of the Beneficial Owners of the ADSs registered in its name. The manner in which a Holder holds ADSs (e.g., in certificated vs. uncertificated form) may affect the rights and obligations of, and the manner in which, and the extent to which, the services are made available to, Holders pursuant to the terms of the Deposit Agreement.

Section 1.26 "Partial Entitlement ADR(s)", "Partial Entitlement ADS(s)" and "Partial Entitlement Share(s)" shall have the respective meanings set forth in Section 2.12.

Section 1.27 "Pounds", "Pence" and "£" shall refer to the lawful currency of England.

Section 1.28 "Principal Office" shall mean, when used with respect to the Depositary, the principal office of the Depositary at which at any particular time its depositary receipts business shall be administered, which, at the date of the Deposit Agreement, is located at 388 Greenwich Street, New York, New York 10013, U.S.A.

Section 1.29 "Registrar" shall mean the Depositary or any bank or trust company having an office in the Borough of Manhattan, The City of New York, which shall be appointed by the Depositary to register issuances, transfers and cancellations of ADSs as herein provided, and shall include any co-registrar appointed by the Depositary for such purposes. Registrars (other than the Depositary) may be removed and substitutes appointed by the Depositary. Each Registrar (other than the Depositary) appointed pursuant to the Deposit Agreement shall be required to give notice in writing to the Depositary accepting such appointment and agreeing to be bound by the applicable terms of the Deposit Agreement.

Section 1.30 "Restricted Securities" shall mean Shares, Deposited Securities or ADSs which (i) have been acquired directly or indirectly from the Company or any of its Affiliates in a transaction or chain of transactions not involving any public offering and are subject to resale limitations under the Securities Act or the rules issued thereunder, or (ii) are held by an executive officer or director (or persons performing similar functions) or other Affiliate of the Company, or (iii) are subject to other restrictions on sale or deposit under the laws of the United States, England and Wales, or under a shareholder agreement or the Articles of Association of the Company or under the regulations of an applicable securities exchange unless, in each case, such Shares,

Deposited Securities or ADSs are being transferred or sold to persons other than an Affiliate of the Company in a transaction (a) covered by an effective resale registration statement, or (b) exempt from the registration requirements of the Securities Act (as hereinafter defined), and the Shares, Deposited Securities or ADSs are not, when held by such person(s), Restricted Securities.

Section 1.31 "Restricted ADR(s)", "Restricted ADS(s)" and "Restricted Shares" shall have the respective meanings set forth in Section 2.14.

Section 1.32 "Securities Act" shall mean the United States Securities Act of 1933, as amended from time to time.

Section 1.33 "Share Registrar" shall mean Computershare Investor Services plc, a company registered in England and Wales or any other institution organized under the laws of England and Wales appointed by the Company to carry out the duties of registrar for the Shares, and any successor thereto.

Section 1.34 "Shares" shall mean the Company's ordinary shares, with a nominal value of £0.10 per share, validly issued and outstanding and fully paid and may, if the Depositary so agrees after consultation with the Company, include evidence of the right to receive Shares; provided that in no event shall Shares include evidence of the right to receive Shares with respect to which the full purchase price has not been paid or Shares as to which preemptive rights have theretofore not been validly waived or exercised; provided further, however, that, if there shall occur any change in nominal value, split-up, consolidation, reclassification, exchange, conversion or any other event described in Section 4.11 in respect of the Shares of the Company, the term "Shares" shall thereafter, to the maximum extent permitted by law, represent the successor securities resulting from such event.

Section 1.35 "Uncertificated ADS(s)" shall have the meaning set forth in Section 2.13.

Section 1.36 "United States" and "U.S." shall have the meaning assigned to it in Regulation S as promulgated by the Commission under the Securities Act.

ARTICLE II

APPOINTMENT OF DEPOSITARY; FORM OF RECEIPTS; DEPOSIT OF SHARES; EXECUTION AND DELIVERY, TRANSFER AND SURRENDER OF RECEIPTS

Section 2.1 Appointment of Depositary. The Company hereby appoints the Depositary as depositary for the Deposited Property and hereby authorizes and directs the Depositary to act in accordance with the terms and conditions set forth in the Deposit Agreement and the applicable ADRs. Each Holder and each Beneficial Owner, upon acceptance of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement shall be deemed for all purposes to (a) be a party to and bound by the terms of the Deposit Agreement and the applicable ADR(s), and (b) appoint the Depositary its attorney-in-fact, with full power to delegate, to act on its behalf and to take any and all actions contemplated in the Deposit Agreement and the applicable ADR(s), to adopt any and all procedures necessary to

comply with applicable law and to take such action as the Depositary in its sole discretion may deem necessary or appropriate to carry out the purposes of the Deposit Agreement and the applicable ADR(s), the taking of such actions to be the conclusive determinant of the necessity and appropriateness thereof.

Section 2.2 Form and Transferability of ADSs.

(a) **Form.** Certificated ADSs shall be evidenced by definitive ADRs which shall be engraved, printed, lithographed or produced in such other manner as may be agreed upon by the Company and the Depositary. ADRs may be issued under the Deposit Agreement in denominations of any whole number of ADSs. The ADRs shall be substantially in the form set forth in Exhibit A to the Deposit Agreement, with any appropriate insertions, modifications and omissions, in each case as otherwise contemplated in the Deposit Agreement or required by law. ADRs shall be (i) dated, (ii) signed by the manual or facsimile signature of a duly authorized signatory of the Depositary, (iii) countersigned by the manual or facsimile signature of a duly authorized signatory of the Registrar, and (iv) registered in the books maintained by the Registrar for the registration of issuances and transfers of ADSs. No ADR and no Certificated ADS evidenced thereby shall be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company, unless such ADR shall have been so dated, signed, countersigned and registered. ADRs bearing the facsimile signature of a duly-authorized signatory of the Depositary or the Registrar, who at the time of signature was a duly-authorized signatory of the Depositary or the Registrar, as the case may be, shall bind the Depositary, notwithstanding the fact that such signatory has ceased to be so authorized prior to the Delivery of such ADR by the Depositary. The ADRs shall bear a CUSIP number that is different from any CUSIP number that was, is or may be assigned to any depositary receipts previously or subsequently issued pursuant to any other arrangement between the Depositary (or any other depositary) and the Company and which are not ADRs outstanding hereunder.

(b) **Legends.** The ADRs may be endorsed with, or have incorporated in the text thereof, such legends or recitals not inconsistent with the provisions of the Deposit Agreement as may be (i) necessary to enable the Depositary and the Company to perform their respective obligations hereunder, (ii) required to comply with any applicable laws or regulations, or with the rules and regulations of any securities exchange or market upon which ADSs may be traded, listed or quoted, or to conform with any usage with respect thereto, (iii) necessary to indicate any special limitations or restrictions to which any particular ADRs or ADSs are subject by reason of the date of issuance of the Deposited Securities or otherwise, or (iv) required by any book-entry system in which the ADSs are held. Holders and Beneficial Owners shall be deemed, for all purposes, to have notice of, and to be bound by, the terms and conditions of the legends set forth, in the case of Holders, on the ADR registered in the name of the applicable Holders or, in the case of Beneficial Owners, on the ADR representing the ADSs owned by such Beneficial Owners.

(c) **Title.** Subject to the limitations contained herein and in the ADR, title to an ADR (and to each Certificated ADS evidenced thereby) shall be transferable upon the same terms as a certificated security under the laws of the State of New York, provided that, in the case of Certificated ADSs, such ADR has been properly endorsed or is accompanied by proper instruments of transfer. Notwithstanding any notice to the contrary, the Depositary and the

Company may deem and treat the Holder of an ADS (that is, the person in whose name an ADS is registered on the books of the Depositary) as the absolute owner thereof for all purposes. Neither the Depositary nor the Company shall have any obligation nor be subject to any liability under the Deposit Agreement or any ADR to any holder or any Beneficial Owner unless, in the case of a holder of ADSs, such holder is the Holder registered on the books of the Depositary or, in the case of a Beneficial Owner, such Beneficial Owner, or the Beneficial Owner's representative, is the Holder registered on the books of the Depositary.

(d) **Book-Entry Systems.** The Depositary shall make arrangements for the acceptance of the ADSs into DTC. All ADSs held through DTC will be registered in the name of the nominee for DTC (currently "Cede & Co."). The nominee of DTC will be the only "Holder" of all ADSs held through DTC. Unless issued by the Depositary as Uncertificated ADSs, the ADSs registered in the name of Cede & Co. will be evidenced by one or more ADR(s) in the form of a "Balance Certificate," which will provide that it represents the aggregate number of ADSs from time to time indicated in the records of the Depositary as being issued hereunder and that the aggregate number of ADSs represented thereby may from time to time be increased or decreased by making adjustments on such records of the Depositary and of DTC or its nominee as hereinafter provided. Citibank, N.A. (or such other entity as is appointed by DTC or its nominee) may hold the "Balance Certificate" as custodian for DTC. Each Beneficial Owner of ADSs held through DTC must rely upon the procedures of DTC and the DTC Participants to exercise or be entitled to any rights attributable to such ADSs. The DTC Participants shall for all purposes be deemed to have all requisite power and authority to act on behalf of the Beneficial Owners of the ADSs held in the DTC Participants' respective accounts in DTC and the Depositary shall for all purposes be authorized to rely upon any instructions and information given to it by DTC Participants. So long as ADSs are held through DTC or unless otherwise required by law, ownership of beneficial interests in the ADSs registered in the name of the nominee for DTC will be shown on, and transfers of such ownership will be effected only through, records maintained by (i) DTC or its nominee (with respect to the interests of DTC Participants), or (ii) DTC Participants or their nominees (with respect to the interests of clients of DTC Participants). Any distributions made, and any notices given, by the Depositary to DTC under the terms of the Deposit Agreement shall (unless otherwise specified by the Depositary) satisfy the Depositary's obligations under the Deposit Agreement to make such distributions, and give such notices, in respect of the ADSs held in DTC (including, for avoidance of doubt, to the DTC Participants holding the ADSs in their DTC accounts and to the Beneficial Owners of such ADSs).

Section 2.3 Deposit of Shares. Subject to the terms and conditions of the Deposit Agreement and applicable law, Shares or evidence of rights to receive Shares (other than Restricted Securities) may be deposited by any person (including the Depositary in its individual capacity but subject, however, in the case of the Company or any Affiliate of the Company, to Section 5.7) at any time, whether or not the transfer books of the Company or the Share Registrar, if any, are closed, by Delivery of the Shares to the Custodian. Every deposit of Shares shall be accompanied by the following: (A) (i) *in the case of Shares represented by certificates issued in registered form*, the certificate(s) representing such Shares and, where relevant, appropriate instruments of transfer or endorsement, in a form reasonably satisfactory to the Custodian, (ii) *in the case of Shares represented by certificates in bearer form*, the requisite coupons and talons pertaining thereto, and (iii) *in the case of Shares delivered by book-entry transfer and recordation*,

confirmation of such book-entry transfer and recordation in the books of the Share Registrar or of CREST, as applicable, to the Custodian or that irrevocable instructions have been given to cause such Shares to be so issued or transferred, as applicable, and recorded, (B) such certifications and payments (including, without limitation, the Depositary's fees and related charges) and evidence of such payments (including, without limitation, stamping or otherwise marking such Shares by way of receipt) as may be reasonably required by the Depositary or the Custodian in accordance with the provisions of the Deposit Agreement and applicable law, (C) if the Depositary so requires, a written order directing the Depositary to issue and deliver to, or upon the written order of, the person(s) stated in such order the number of ADSs representing the Shares so deposited, (D) evidence reasonably satisfactory to the Depositary (which may be an opinion of counsel) that all necessary approvals have been granted by, or there has been compliance with the rules and regulations of, any applicable governmental agency in England and Wales, and (E) if the Depositary so requires, (i) an agreement, assignment or instrument reasonably satisfactory to the Depositary or the Custodian which provides for the prompt transfer by any person in whose name the Shares are or have been recorded to the Custodian of any distribution, or right to subscribe for additional Shares or to receive other property in respect of any such deposited Shares or, in lieu thereof, such indemnity or other agreement as shall be reasonably satisfactory to the Depositary or the Custodian and (ii) if the Shares are registered in the name of the person on whose behalf they are presented for deposit, a proxy or proxies entitling the Custodian to exercise voting rights in respect of the Shares for any and all purposes until the Shares so deposited are registered in the name of the Depositary, the Custodian or any nominee.

Without limiting any other provision of the Deposit Agreement, the Depositary shall instruct the Custodian not to, and the Depositary shall not knowingly, accept for deposit (a) any Restricted Securities (except as contemplated by Section 2.14) nor (b) any fractional Shares or fractional Deposited Securities nor (c) a number of Shares or Deposited Securities which upon application of the ADS to Shares ratio would give rise to fractional ADSs. No Shares shall be accepted for deposit unless accompanied by evidence, if any is required by the Depositary, that is reasonably satisfactory to the Depositary or the Custodian that all conditions to such deposit have been satisfied by the person depositing such Shares under the laws and regulations of England and Wales and any necessary approval has been granted by any applicable governmental body in England and Wales, if any. The Depositary may issue ADSs against evidence of rights to receive Shares from the Company, any agent of the Company or any custodian, registrar, transfer agent, clearing agency or other entity involved in ownership or transaction records in respect of the Shares. Such evidence of rights shall consist of written blanket or specific guarantees of ownership of Shares furnished by the Company or any such custodian, registrar, transfer agent, clearing agency or other entity involved in ownership or transaction records in respect of the Shares.

Without limitation of the foregoing, the Depositary shall not knowingly accept for deposit under the Deposit Agreement (A) any Shares or other securities required to be registered under the provisions of the Securities Act, unless (i) a registration statement is in effect as to such Shares or other securities or (ii) the deposit is made upon terms contemplated in Section 2.14, or (B) any Shares or other securities the deposit of which would violate any provisions of the Articles of Association of the Company or English law. For purposes of the foregoing sentence, the Depositary shall be entitled to rely upon representations and warranties made or deemed made

pursuant to the Deposit Agreement and shall not be required to make any further investigation. The Depositary will comply with written instructions of the Company (received by the Depositary reasonably in advance) not to accept for deposit hereunder any Shares identified in such instructions at such times and under such circumstances as may reasonably be specified in such instructions in order to facilitate the Company's compliance with the securities laws of the United States.

Section 2.4 Registration and Safekeeping of Deposited Securities. The Depositary shall instruct the Custodian upon each Delivery of registered Shares being deposited hereunder with the Custodian (or other Deposited Securities pursuant to Article IV hereof), together with the other documents above specified, to present such Shares, together with the appropriate instrument(s) of transfer or endorsement, duly stamped, to the Share Registrar for transfer and registration of the Shares (as soon as transfer and registration can be accomplished and at the expense of the person for whom the deposit is made) in the name of the Depositary, the Custodian or a nominee of either. Deposited Securities shall be held by the Depositary, or by a Custodian for the account and to the order of the Depositary or a nominee of the Depositary, in each case, on behalf of the Holders and Beneficial Owners, at such place(s) as the Depositary or the Custodian shall determine. Notwithstanding anything else contained in the Deposit Agreement, any ADR(s), or any other instruments or agreements relating to the ADSs and the corresponding Deposited Property, the registration of the Deposited Securities in the name of the Depositary, the Custodian or any of their respective nominees, shall, to the maximum extent permitted by applicable law, vest in the Depositary, the Custodian or the applicable nominee the record ownership in the applicable Deposited Securities with the beneficial ownership rights and interests in such Deposited Securities being at all times vested with the Beneficial Owners of the ADSs representing the Deposited Securities. Notwithstanding the foregoing, the Depositary, the Custodian and the applicable nominee shall at all times be entitled to exercise the beneficial ownership rights in all Deposited Property, in each case only on behalf of the Holders and Beneficial Owners of the ADSs representing the Deposited Property, upon the terms set forth in the Deposit Agreement and, if applicable, the ADR(s) representing the ADSs. The Depositary, the Custodian and their respective nominees shall for all purposes be deemed to have all requisite power and authority to act in respect of Deposited Property on behalf of the Holders and Beneficial Owners of ADSs representing the Deposited Property, and upon making payments to, or acting upon instructions from, or information provided by, the Depositary, the Custodian or their respective nominees all persons shall be authorized to rely upon such power and authority

Section 2.5 Issuance of ADSs. The Depositary has made arrangements with the Custodian for the Custodian to confirm to the Depositary upon receipt of a deposit of Shares (i) that a deposit of Shares has been made pursuant to Section 2.3, (ii) that such Deposited Securities have been recorded in the name of the Depositary, the Custodian or a nominee of either on the shareholders' register maintained by or on behalf of the Company by the Share Registrar on the books of CREST, (iii) that all required documents have been received, and (iv) the person(s) to whom or upon whose order ADSs are deliverable in respect thereof and the number of ADSs to be so delivered. Such notification may be made by letter, cable, telex, SWIFT message or, at the risk and expense of the person making the deposit, by facsimile or other means of electronic transmission. Upon receiving such notice from the Custodian, the Depositary, subject to the terms and conditions of the Deposit Agreement and applicable law, shall issue the ADSs representing the

Shares so deposited to or upon the order of the person(s) named in the notice delivered to the Depositary and, if applicable, shall execute and deliver at its Principal Office Receipt(s) registered in the name(s) requested by such person(s) and evidencing the aggregate number of ADSs to which such person(s) are entitled, but, in each case, only upon payment to the Depositary of the charges of the Depositary for accepting a deposit of Shares and issuing ADSs (as set forth in Section 5.9 and Exhibit B hereto) and all taxes and governmental charges and fees payable in connection with such deposit and the transfer of the Shares and the issuance of the ADS(s). The Depositary shall only issue ADSs in whole numbers and deliver, if applicable, ADR(s) evidencing whole numbers of ADSs.

Section 2.6 Transfer, Combination and Split-up of ADRs.

(a) **Transfer.** The Registrar shall register the transfer of ADRs (and of the ADSs represented thereby) on the books maintained for such purpose and the Depositary shall (x) cancel such ADRs and execute new ADRs evidencing the same aggregate number of ADSs as those evidenced by the ADRs canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs and (z) Deliver such new ADRs to or upon the order of the person entitled thereto, if each of the following conditions has been satisfied: (i) the ADRs have been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a transfer thereof, (ii) the surrendered ADRs have been properly endorsed or are accompanied by proper instruments of transfer (including signature guarantees in accordance with standard securities industry practice), (iii) the surrendered ADRs have been duly stamped (if required by the laws of the State of New York or of the United States), and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B hereto) have been paid, *subject, however, in each case,* to the terms and conditions of the applicable ADRs, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

(b) **Combination & Split-Up.** The Registrar shall register the split-up or combination of ADRs (and of the ADSs represented thereby) on the books maintained for such purpose and the Depositary shall (x) cancel such ADRs and execute new ADRs for the number of ADSs requested, but in the aggregate not exceeding the number of ADSs evidenced by the ADRs canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs and (z) Deliver such new ADRs to or upon the order of the Holder thereof, if each of the following conditions has been satisfied: (i) the ADRs have been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a split-up or combination thereof, and (ii) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B hereto) have been paid, *subject, however, in each case*, to the terms and conditions of the applicable ADRs, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

Section 2.7 Surrender of ADSs and Withdrawal of Deposited Securities. The Holder of ADSs shall be entitled to Delivery (at the Custodian's designated office) of the Deposited Securities at the time represented by the ADSs upon satisfaction of each of the following conditions: (i) the Holder (or a duly-authorized attorney of the Holder) has duly Delivered ADSs to the Depositary at its Principal Office (and if applicable, the ADRs evidencing such ADSs) for the purpose of withdrawal of the Deposited Securities represented thereby, (ii) if applicable and so required by the Depositary, the ADRs Delivered to the Depositary for such purpose have been properly endorsed in blank or are accompanied by proper instruments of transfer in blank (including signature guarantees in accordance with standard securities industry practice), (iii) if so required by the Depositary, the Holder of the ADSs has executed and delivered to the Depositary a written order directing the Depositary to cause the Deposited Securities being withdrawn to be Delivered to or upon the written order of the person(s) designated in such order, and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B) have been paid, *subject, however, in each case*, to the terms and conditions of the ADRs evidencing the surrendered ADSs, of the Deposit Agreement, of the Company's Articles of Association and of any applicable laws and the rules of CREST, and to any provisions of or governing the Deposited Securities , in each case as in effect at the time thereof.

Upon satisfaction of each of the conditions specified above, the Depositary (i) shall cancel the ADSs Delivered to it (and, if applicable, the ADR(s) evidencing the ADSs so Delivered), (ii) shall direct the Registrar to record the cancellation of the ADSs so Delivered on the books maintained for such purpose, and (iii) shall direct the Custodian to Deliver, or cause the Delivery of, in each case, without unreasonable delay, the Deposited Securities represented by the ADSs so canceled together with any certificate or other document of title for the Deposited Securities, or evidence of the electronic transfer thereof (if available), as the case may be, to or upon the written order of the person(s) designated in the order delivered to the Depositary for such purpose, *subject however, in each case*, to the terms and conditions of the Deposit Agreement, of the ADRs evidencing the ADSs so canceled, of the Articles of Association of the Company, of any applicable laws and of the rules of CREST, and to the terms and conditions of or governing the Deposited Securities, in each case as in effect at the time thereof.

The Depositary shall not accept for surrender ADSs representing less than one (1) Share. In the case of Delivery to it of ADSs representing a number other than a whole number of Shares, the Depositary shall cause ownership of the appropriate whole number of Shares to be Delivered in accordance with the terms hereof, and shall, at the discretion of the Depositary, either (i) return to the person surrendering such ADSs the number of ADSs representing any remaining fractional Share, or (ii) sell or cause to be sold the fractional Share represented by the ADSs so surrendered and remit the proceeds of such sale (net of (a) applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld as a result of such sale) to the person surrendering the ADSs.

Notwithstanding anything else contained in any ADR or the Deposit Agreement, the Depositary may make delivery at the Principal Office of the Depositary of Deposited Property consisting of (i) any cash dividends or cash distributions, or (ii) any proceeds from the sale of any non-cash distributions, which are at the time held by the Depositary in respect of the Deposited

Securities represented by the ADSs surrendered for cancellation and withdrawal. At the request, risk and expense of any Holder so surrendering ADSs, and for the account of such Holder, the Depositary shall direct the Custodian to forward (to the extent permitted by law) any Deposited Property (other than Deposited Securities) held by the Custodian in respect of such ADSs to the Depositary for delivery at the Principal Office of the Depositary. Such direction shall be given by letter or, at the request, risk and expense of such Holder, by cable, telex or facsimile transmission.

Section 2.8 Limitations on Execution and Delivery, Transfer, etc. of ADSs; Suspension of Delivery, Transfer, etc.

(a) **Additional Requirements.** As a condition precedent to the execution and Delivery, the registration of issuance, transfer, split-up, combination or surrender, of any ADS, the delivery of any distribution thereon, or the withdrawal of any Deposited Property, the Depositary or the Custodian may require (i) payment from the depositor of Shares or presenter of ADSs or of an ADR of a sum sufficient to reimburse it for any tax or other governmental charge and any stock transfer or registration fee with respect thereto (including any such tax or charge and fee with respect to Shares being deposited or withdrawn) and payment of any applicable fees and charges of the Depositary as provided in Section 5.9 and Exhibit B, (ii) the production of proof reasonably satisfactory to it as to the identity and genuineness of any signature or any other matter contemplated by Section 3.1, and (iii) compliance with (A) any laws or governmental regulations relating to the execution and Delivery of ADRs or ADSs or to the withdrawal of Deposited Securities and (B) such reasonable regulations as the Depositary and the Company may establish consistent with the provisions of the representative ADR, if applicable, the Deposit Agreement and applicable law.

(b) **Additional Limitations.** The issuance of ADSs against deposits of Shares generally or against deposits of particular Shares may be suspended, or the deposit of particular Shares may be refused, or the registration of transfer of ADSs in particular instances may be refused, or the registration of transfers of ADSs generally may be suspended, during any period when the transfer books of the Company, the Depositary, a Registrar or the Share Registrar are closed or if any such action is deemed necessary or advisable by the Depositary or the Company, in good faith, at any time or from time to time because of any requirement of law or regulation, any government or governmental body or commission or any securities exchange on which the ADSs or Shares are listed, or under any provision of the Deposit Agreement or the representative ADR(s), if applicable, or under any provision of, or governing, the Deposited Securities, or because of a meeting of shareholders of the Company or for any other reason, subject, in all cases, to Section 7.8(a).

(c) **Regulatory Restrictions.** Notwithstanding any provision of the Deposit Agreement or any ADR(s) to the contrary, Holders are entitled to surrender outstanding ADSs to withdraw the Deposited Securities associated herewith at any time subject only to (i) temporary delays caused by closing the transfer books of the Depositary or the Company or the deposit of Shares in connection with voting at a shareholders' meeting or the payment of dividends, (ii) the payment of fees, taxes and similar charges, (iii) compliance with any U.S. or foreign laws or governmental regulations relating to the ADSs or to the withdrawal of the Deposited Securities, and (iv) other circumstances specifically contemplated by Instruction I.A.(l) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time).

Section 2.9 Lost ADRs, etc. In case any ADR shall be mutilated, destroyed, lost, or stolen, the Depositary shall execute and deliver a new ADR of like tenor at the expense of the Holder (a) *in the case of a mutilated ADR*, in exchange of and substitution for such mutilated ADR upon cancellation thereof, or (b) *in the case of a destroyed, lost or stolen ADR*, in lieu of and in substitution for such destroyed, lost, or stolen ADR, after the Holder thereof (i) has submitted to the Depositary a written request for such exchange and substitution before the Depositary has notice that the ADR has been acquired by a bona fide purchaser, (ii) has provided such security or indemnity (including an indemnity bond) as may be required by the Depositary to save it and any of its agents harmless, and (iii) has satisfied any other reasonable requirements imposed by the Depositary, including, without limitation, evidence satisfactory to the Depositary of such destruction, loss or theft of such ADR, the authenticity thereof and the Holder's ownership thereof.

Section 2.10 Cancellation and Destruction of Surrendered ADRs; Maintenance of Records. All ADRs surrendered to the Depositary shall be canceled by the Depositary. Canceled ADRs shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable against the Depositary for any purpose. The Depositary is authorized to destroy ADRs so canceled, provided the Depositary maintains a record of all destroyed ADRs. Any ADSs held in book-entry form (*e.g.*, through accounts at DTC) shall be deemed canceled when the Depositary causes the number of ADSs evidenced by the Balance Certificate to be reduced by the number of ADSs surrendered (without the need to physically destroy the Balance Certificate).

Section 2.11 Escheatment. In the event any unclaimed property relating to the ADSs, for any reason, is in the possession of Depositary and has not been claimed by the Holder thereof or cannot be delivered to the Holder thereof through usual channels, the Depositary shall, upon expiration of any applicable statutory period relating to abandoned property laws, escheat such unclaimed property to the relevant authorities in accordance with the laws of each of the relevant States of the United States.

Section 2.12 Partial Entitlement ADSs. In the event any Shares are deposited which (i) entitle the holders thereof to receive a per-share distribution or other entitlement in an amount different from the Shares then on deposit or (ii) are not fully fungible (including, without limitation, as to settlement or trading) with the Shares then on deposit (the Shares then on deposit collectively, "Full Entitlement Shares" and the Shares with different entitlement, "Partial Entitlement Shares"), the Depositary shall (i) cause the Custodian to hold Partial Entitlement Shares separate and distinct from Full Entitlement Shares, and (ii) subject to the terms of the Deposit Agreement, issue ADSs representing Partial Entitlement Shares which are separate and distinct from the ADSs representing Full Entitlement Shares, by means of separate CUSIP numbering and legending (if necessary) and, if applicable, by issuing ADRs evidencing such ADSs with applicable notations thereon ("Partial Entitlement ADSs/ADRs" and "Full Entitlement ADSs/ADRs", respectively). If and when Partial Entitlement Shares become Full Entitlement Shares, the Depositary shall (a) give notice thereof to Holders of Partial Entitlement ADSs and give Holders of Partial Entitlement ADRs the opportunity to exchange such Partial Entitlement ADRs for Full Entitlement ADRs, (b) cause the Custodian to transfer the Partial Entitlement Shares into the account of the Full Entitlement Shares, and (c) take such actions as are necessary to

remove the distinctions between (i) the Partial Entitlement ADRs and ADSs, on the one hand, and (ii) the Full Entitlement ADRs and ADSs on the other. Holders and Beneficial Owners of Partial Entitlement ADSs shall only be entitled to the entitlements of Partial Entitlement Shares. Holders and Beneficial Owners of Full Entitlement ADSs shall be entitled only to the entitlements of Full Entitlement Shares. All provisions and conditions of the Deposit Agreement shall apply to Partial Entitlement ADRs and ADSs to the same extent as Full Entitlement ADRs and ADSs, except as contemplated by this Section 2.12. The Depositary is authorized to take any and all other actions as may be necessary (including, without limitation, making the necessary notations on ADRs) to give effect to the terms of this Section 2.12. The Company agrees to give timely written notice to the Depositary if any Shares issued or to be issued are Partial Entitlement Shares and shall assist the Depositary with the establishment of procedures enabling the identification of Partial Entitlement Shares upon Delivery to the Custodian.

Section 2.13 Certificated/Uncertificated ADSs. Notwithstanding any other provision of the Deposit Agreement, the Depositary may, at any time and from time to time, issue ADSs that are not evidenced by ADRs (such ADSs, the "Uncertificated ADS(s)" and the ADS(s) evidenced by ADR(s), the "Certificated ADS(s)"). When issuing and maintaining Uncertificated ADS(s) under the Deposit Agreement, the Depositary shall at all times be subject to (i) the standards applicable to registrars and transfer agents maintaining direct registration systems for equity securities in New York and issuing uncertificated securities under New York law, and (ii) the terms of New York law applicable to uncertificated equity securities. Uncertificated ADSs shall not be represented by any instruments but shall be evidenced by registration in the books of the Depositary maintained for such purpose. Holders of Uncertificated ADSs, that are not subject to any registered pledges, liens, restrictions or adverse claims of which the Depositary has notice at such time, shall at all times have the right to exchange the Uncertificated ADS(s) for Certificated ADS(s) of the same type and class, subject in each case to (x) the applicable laws and any rules and regulations the Depositary may have established in respect of the Uncertificated ADSs, and (y) the continued availability of Certificated ADSs in the U.S. Holders of Certificated ADSs shall, if the Depositary maintains a direct registration system for the ADSs, have the right to exchange the Certificated ADSs for Uncertificated ADSs upon (i) the due surrender of the Certificated ADS(s) to the Depositary for such purpose and (ii) the presentation of a written request to that effect to the Depositary, subject in each case to (a) all liens and restrictions noted on the ADR evidencing the Certificated ADS(s) and all adverse claims of which the Depositary then has notice, (b) the terms of the Deposit Agreement and the rules and regulations that the Depositary may establish for such purposes hereunder, (c) applicable law, and (d) payment of the Depositary fees and expenses applicable to such exchange of Certificated ADS(s) for Uncertificated ADS(s). Uncertificated ADSs shall in all material respects be identical to Certificated ADS(s) of the same type and class, except that (i) no ADR(s) shall be, or shall need to be, issued to evidence Uncertificated ADS(s), (ii) Uncertificated ADS(s) shall, subject to the terms of the Deposit Agreement, be transferable upon the same terms and conditions as uncertificated securities under New York law, (iii) the ownership of Uncertificated ADS(s) shall be recorded on the books of the Depositary maintained for such purpose and evidence of such ownership shall be reflected in periodic statements provided by the Depositary to the Holder(s) in accordance with applicable New York law, (iv) the Depositary may from time to time, upon notice to the Holders of Uncertificated ADSs affected thereby, establish rules and regulations, and amend or supplement existing rules and regulations, as may be deemed reasonably necessary to maintain Uncertificated ADS(s) on behalf of Holders,

provided that (a) such rules and regulations do not conflict with the terms of the Deposit Agreement and applicable law, and (b) the terms of such rules and regulations are readily available to Holders upon request, (v) the Uncertificated ADS(s) shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company unless such Uncertificated ADS(s) is/are registered on the books of the Depositary maintained for such purpose, (vi) the Depositary may, in connection with any deposit of Shares resulting in the issuance of Uncertificated ADSs and with any transfer, pledge, release and cancellation of Uncertificated ADSs, require the prior receipt of such documentation as the Depositary may deem reasonably appropriate, and (vii) upon termination of the Deposit Agreement, the Depositary shall not require Holders of Uncertificated ADSs to affirmatively instruct the Depositary before remitting proceeds from the sale of the Deposited Property represented by such Holders' Uncertificated ADSs under the terms of Section 6.2 of the Deposit Agreement. When issuing ADSs under the terms of the Deposit Agreement, including, without limitation, issuances pursuant to Sections 2.5, 4.2, 4.3, 4.4, 4.5 and 4.11, the Depositary may in its discretion determine to issue Uncertificated ADSs rather than Certificated ADSs, unless otherwise specifically instructed by the applicable Holder to issue Certificated ADSs. All provisions and conditions of the Deposit Agreement shall apply to Uncertificated ADSs to the same extent as to Certificated ADSs, except as contemplated by this Section 2.13. The Depositary is authorized and directed to take any and all actions and establish any and all procedures deemed reasonably necessary to give effect to the terms of this Section 2.13. Any references in the Deposit Agreement or any ADR(s) to the terms "American Depositary Share(s)" or "ADS(s)" shall, unless the context otherwise requires, include Certificated ADS(s) and Uncertificated ADS(s). Except as set forth in this Section 2.13 and except as required by applicable law, the Uncertificated ADSs shall be treated as ADSs issued and outstanding under the terms of the Deposit Agreement. In the event that, in determining the rights and obligations of parties hereto with respect to any Uncertificated ADSs, any conflict arises between (a) the terms of the Deposit Agreement (other than this Section 2.13) and (b) the terms of this Section 2.13, the terms and conditions set forth in this Section 2.13 shall be controlling and shall govern the rights and obligations of the parties to the Deposit Agreement pertaining to the Uncertificated ADSs.

Section 2.14 Restricted ADSs. The Depositary shall, at the request and expense of the Company, establish procedures enabling the deposit hereunder of Shares that are Restricted Securities in order to enable the holder of such Shares to hold its ownership interests in such Restricted Securities in the form of ADSs issued under the terms hereof (such Shares, "Restricted Shares"). Upon receipt of a written request from the Company to accept Restricted Shares for deposit hereunder, the Depositary agrees to establish procedures permitting the deposit of such Restricted Shares and the issuance of ADSs representing the right to receive, subject to the terms of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS), such deposited Restricted Shares (such ADSs, the "Restricted ADSs," and the ADRs evidencing such Restricted ADSs, the "Restricted ADRs"). Notwithstanding anything contained in this Section 2.14, the Depositary and the Company may, to the extent not prohibited by law, agree to issue the Restricted ADSs in uncertificated form ("Uncertificated Restricted ADSs") upon such terms and conditions as the Company and the Depositary may deem necessary and appropriate. The Company shall assist the Depositary in the establishment of such procedures and agrees that it shall take all steps necessary and satisfactory to the Depositary to ensure that the establishment of such procedures does not violate the provisions of the Securities Act or any other applicable laws.

The depositors of such Restricted Shares and the Holders of the Restricted ADSs may be required prior to the deposit of such Restricted Shares, the transfer of the Restricted ADRs and Restricted ADSs or the withdrawal of the Restricted Shares represented by Restricted ADSs to provide such written certifications or agreements as the Depositary or the Company may require. The Company shall provide to the Depositary in writing the legend(s) to be affixed to the Restricted ADRs (if the Restricted ADSs are to be issued as Certificated ADSs**)**, or to be included in the statements issued from time to time to Holders of Uncertificated ADSs (if issued as Uncertificated Restricted ADSs), which legends shall (i) be in a form reasonably satisfactory to the Depositary and (ii) contain the specific circumstances under which the Restricted ADSs, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, may be transferred or the Restricted Shares withdrawn. The Restricted ADSs issued upon the deposit of Restricted Shares shall be separately identified on the books of the Depositary and the Restricted Shares so deposited shall, to the extent required by law, be held separate and distinct from the other Deposited Securities held hereunder. The Restricted ADSs shall not be eligible for inclusion in any book-entry settlement system, including, without limitation, DTC, and shall not in any way be fungible with the ADSs issued under the terms hereof that are not Restricted ADSs. The Restricted ADSs, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, shall be transferable only by the Holder thereof upon delivery to the Depositary of (i) all documentation otherwise contemplated by the Deposit Agreement and (ii) an opinion of counsel satisfactory to the Depositary setting forth, *inter alia*, the conditions upon which the Restricted ADSs presented, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, are transferable by the Holder thereof under applicable securities laws and the transfer restrictions contained in the legend applicable to the Restricted ADSs presented for transfer. Except as set forth in this Section 2.14 and except as required by applicable law, the Restricted ADSs and the Restricted ADRs evidencing Restricted ADSs shall be treated as ADSs and ADRs issued and outstanding under the terms of the Deposit Agreement. In the event that, in determining the rights and obligations of parties hereto with respect to any Restricted ADSs, any conflict arises between (a) the terms of the Deposit Agreement (other than this Section 2.14) and (b) the terms of (i) this Section 2.14 or (ii) the applicable Restricted ADR, the terms and conditions set forth in this Section 2.14 and of the Restricted ADR shall be controlling and shall govern the rights and obligations of the parties to the Deposit Agreement pertaining to the deposited Restricted Shares, the Restricted ADSs and Restricted ADRs.

If the Restricted ADRs, the Restricted ADSs and the Restricted Shares cease to be Restricted Securities, the Depositary, upon receipt of (x) an opinion of counsel satisfactory to the Depositary setting forth, *inter alia*, that the Restricted ADRs, the Restricted ADSs and the Restricted Shares are not as of such time Restricted Securities, and (y) instructions from the Company to remove the restrictions applicable to the Restricted ADRs, the Restricted ADSs and the Restricted Shares, shall (i) eliminate the distinctions and separations that may have been established between the applicable Restricted Shares held on deposit under this Section 2.14 and the other Shares held on deposit under the terms of the Deposit Agreement that are not Restricted Shares, (ii) treat the newly unrestricted ADRs and ADSs on the same terms as, and fully fungible with, the other ADRs and ADSs issued and outstanding under the terms of the Deposit Agreement that are not Restricted ADRs or Restricted ADSs, and (iii) take all actions necessary to remove any distinctions, limitations and restrictions previously existing under this Section 2.14 between the applicable Restricted ADRs and Restricted ADSs, respectively, on the one hand, and the other ADRs and ADSs that are not Restricted ADRs or Restricted ADSs, respectively, on the other hand, including, without limitation, by making the newly-unrestricted ADSs eligible for inclusion in the applicable book-entry settlement systems.

ARTICLE III

CERTAIN OBLIGATIONS OF HOLDERS AND BENEFICIAL OWNERS OF ADSs

Section 3.1 Proofs, Certificates and Other Information. Any person presenting Shares for deposit, any Holder and any Beneficial Owner may be required, and every Holder and Beneficial Owner agrees, from time to time to provide to the Depositary and the Custodian such proof of citizenship or residence, taxpayer status, payment of all applicable taxes or other governmental charges, exchange control approval, legal or beneficial ownership of ADSs and Deposited Property, compliance with applicable laws, the terms of the Deposit Agreement or the ADR(s) evidencing the ADSs and the provisions of, or governing, the Deposited Property, to execute such certifications and to make such representations and warranties, and to provide such other information and documentation (or, in the case of Shares in registered form presented for deposit, such information relating to the registration on the books of the Company or of the Share Registrar) as the Depositary or the Custodian may deem necessary or proper or as the Company may reasonably require by written request to the Depositary consistent with its obligations under the Deposit Agreement and the applicable ADR(s). The Depositary and the Registrar, as applicable, may and at the reasonable request of the Company, shall, to the extent practicable and subject to applicable law, withhold the execution or delivery or registration of transfer of any ADR or ADS or the distribution or sale of any dividend or distribution of rights or of the proceeds thereof or, to the extent not limited by the terms of Section 7.8(a), the delivery of any Deposited Property until such proof or other information is filed or such certifications are executed, or such representations and warranties are made, or such other documentation or information provided, in each case to the Depositary's, the Registrar's and the Company's satisfaction. The Depositary shall provide the Company, in a timely manner, with copies or originals if necessary and appropriate of (i) any such proofs of citizenship or residence, taxpayer status, or exchange control approval or copies of written representations and warranties which it receives from Holders and Beneficial Owners, and (ii) any other information or documents which the Company may reasonably request and which the Depositary shall request and receive from any Holder or Beneficial Owner or any person presenting Shares for deposit or ADSs for cancellation, transfer or withdrawal. Nothing herein shall obligate the Depositary to (i) obtain any information for the Company if not provided by the Holders or Beneficial Owners, or (ii) verify or vouch for the accuracy of the information so provided by the Holders or Beneficial Owners.

Section 3.2 Liability for Taxes and Other Charges. Any tax or other governmental charge payable by the Custodian or by the Depositary with respect to any Deposited Property, ADSs or ADRs shall be payable by the Holders and Beneficial Owners to the Depositary. The Company, the Custodian and/or the Depositary may withhold or deduct from any distributions made in respect of Deposited Property, and may sell for the account of a Holder and/or Beneficial Owner any or all of the Deposited Property and apply such distributions and sale proceeds in payment of, any taxes (including applicable interest and penalties) or charges that are or may be payable by Holders or Beneficial Owners in respect of the ADSs, Deposited Property and ADRs,

the Holder and the Beneficial Owner remaining liable for any deficiency. The Custodian may refuse the deposit of Shares and the Depositary may refuse to issue ADSs, to deliver ADRs, register the transfer of ADSs, register the split-up or combination of ADRs and (subject to Section 7.8(a)) the withdrawal of Deposited Property until payment in full of such tax, charge, penalty or interest is received. Every Holder and Beneficial Owner agrees to indemnify the Depositary, the Company, the Custodian, and any of their agents, officers, employees and Affiliates for, and to hold each of them harmless from, any claims with respect to taxes (including applicable interest and penalties thereon) arising from any tax benefit obtained for such Holder and/or Beneficial Owner. The obligations of Holders and Beneficial Owners under this Section 3.2 shall survive any transfer of ADSs, any cancellation of ADSs and withdrawal of Deposited Securities, and the termination of the Deposit Agreement.

Section 3.3 Representations and Warranties on Deposit of Shares. Each person depositing Shares under the Deposit Agreement shall be deemed thereby to represent and warrant that (i) such Shares and the certificates therefor are duly authorized, validly allotted and issued, fully paid, not subject to any call for the payment of further capital and legally obtained by such person, (ii) all preemptive (and similar) rights, if any, with respect to such Shares have been validly waived, disapplied or exercised, (iii) the person making such deposit is duly authorized so to do, (iv) the Shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, (v) the Shares presented for deposit are not, and the ADSs issuable upon such deposit will not be, Restricted Securities (except as contemplated in Section 2.14), (vi) the Shares presented for deposit have not been stripped of any rights or entitlements, and (vii) the deposit of the Shares does not violate any applicable provisions of English law. Such representations and warranties shall survive the deposit and withdrawal of Shares, the issuance and cancellation of ADSs in respect thereof and the transfer of such ADSs. If any such representations or warranties are false in any way, the Company and the Depositary shall be authorized, at the cost and expense of the person depositing Shares, to take any and all actions necessary to correct the consequences thereof.

Section 3.4 Compliance with Information Requests. Notwithstanding any other provision of the Deposit Agreement or any ADR(s), each Holder and Beneficial Owner agrees to comply with requests from the Company pursuant to applicable law, the rules and requirements of any stock exchange on which the Shares or ADSs are, or will be, registered, traded or listed or the Articles of Association of the Company, which are made to provide information, *inter alia*, as to the capacity in which such Holder or Beneficial Owner owns ADSs (and Shares as the case may be) and regarding the identity of any other person(s) interested in such ADSs and the nature of such interest and various other matters, whether or not they are Holders and/or Beneficial Owners at the time of such request. The Depositary agrees to use its reasonable efforts to forward, upon the request of the Company and at the Company's expense, any such request from the Company to the Holders and to forward to the Company, as promptly as practicable, any such responses to such requests received by the Depositary.

Section 3.5 Ownership Restrictions. Notwithstanding any other provision in the Deposit Agreement or any ADR, the Company may restrict transfers of the Shares where such transfer might result in ownership of Shares exceeding limits imposed by applicable law or the Articles of Association of the Company. The Company may also restrict, in such manner as it

deems appropriate, transfers of the ADSs where such transfer may result in the total number of Shares represented by the ADSs owned by a single Holder or Beneficial Owner to exceed any such limits. The Company may, in its sole discretion but subject to applicable law, instruct the Depositary to take action with respect to the ownership interest of any Holder or Beneficial Owner in excess of the limits set forth in the preceding sentence, including, but not limited to, the imposition of restrictions on the transfer of ADSs, the removal or limitation of voting rights or mandatory sale or disposition on behalf of a Holder or Beneficial Owner of the Shares represented by the ADSs held by such Holder or Beneficial Owner in excess of such limitations, if and to the extent such disposition is permitted by applicable law and the Articles of Association of the Company. Nothing herein shall be interpreted as obligating the Depositary or the Company to ensure compliance with the ownership restrictions described in this Section 3.5.

Notwithstanding any provision of the Deposit Agreement or of the ADRs and without limiting the foregoing, by being a Holder of an ADR, each such Holder agrees to provide such information as the Company may request in a disclosure notice (a "Disclosure Notice") given pursuant to the U.K. Companies Act 2006 (as amended from time to time and including any statutory modification or re-enactment thereof, the "Companies Act") or the Articles of Association of the Company. By accepting or holding an ADR, each Holder acknowledges that it understands that failure to comply with a Disclosure Notice may result in the imposition of sanctions against the holder of the Shares in respect of which the non-complying person is or was, or appears to be or has been, interested as provided in the Companies Act and the Articles of Association which currently include, the withdrawal of the voting rights of such Shares and the imposition of restrictions on the rights to receive dividends on and to transfer such Shares.

The Company reserves the right to instruct Holders to deliver their ADSs for cancellation and withdrawal of the Deposited Securities so as to permit the Company to deal directly with the Holder thereof as a holder of Shares and Holders agree to comply with such instructions. The Depositary agrees to cooperate with the Company in its efforts to inform Holders of the Company's exercise of its rights under this paragraph and agrees to consult with, and provide reasonable assistance without risk, liability or expense on the part of the Depositary, to the Company on the manner or manners in which it may enforce such rights with respect to any Holder.

Section 3.6 Reporting Obligations and Regulatory Approvals. Applicable laws and regulations may require holders and beneficial owners of Shares, including the Holders and Beneficial Owners of ADSs, to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. Holders and Beneficial Owners of ADSs are solely responsible for determining and complying with such reporting requirements and obtaining such approvals. Each Holder and each Beneficial Owner hereby agrees to make such determination, file such reports, and obtain such approvals to the extent and in the form required by applicable laws and regulations as in effect from time to time. Neither the Depositary, the Custodian, the Company or any of their respective agents or affiliates shall be required to take any actions whatsoever on behalf of Holders or Beneficial Owners to determine or satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

ARTICLE IV

THE DEPOSITED SECURITIES

Section 4.1 Cash Distributions. Whenever the Company intends to make a distribution of a cash dividend or other cash distribution in respect of any Deposited Securities, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable for determining the holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt of such notice, the Depositary shall establish an ADS Record Date upon the terms described in Section 4.9. Upon receipt of confirmation of the receipt of (x) any cash dividend or other cash distribution on any Deposited Securities, or (y) proceeds from the sale of any Deposited Property held in respect of the ADSs under the terms hereof, the Depositary will (i) if at the time of receipt thereof any amounts received in a Foreign Currency can, in the judgment of the Depositary (pursuant to Section 4.8), be converted on a practicable basis into Dollars transferable to the United States, promptly convert or cause to be converted such cash dividend, distribution or proceeds into Dollars (on the terms described in Section 4.8), (ii) if applicable and unless previously established, establish the ADS Record Date upon the terms described in Section 4.9, and (iii) distribute promptly the amount thus received (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld in connection with the distribution) to the Holders entitled thereto as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date. The Depositary shall distribute only such amount, however, as can be distributed without attributing to any Holder a fraction of one cent, and any balance not so distributed shall be held by the Depositary (without liability for interest thereon) and shall be added to and become part of the next sum received by the Depositary for distribution to Holders of ADSs outstanding at the time of the next distribution. If the Company, the Custodian or the Depositary is required to withhold and does withhold from any cash dividend or other cash distribution in respect of any Deposited Securities, or from any cash proceeds from the sales of Deposited Property, an amount on account of taxes, duties or other governmental charges, the amount distributed to Holders on the ADSs shall be reduced accordingly. Such withheld amounts shall be forwarded by the Company, the Custodian or the Depositary to the relevant governmental authority. Evidence of payment thereof by the Company shall be forwarded by the Company to the Depositary upon request. The Depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable Holders and Beneficial Owners of ADSs until the distribution can be effected or the funds that the Depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.1, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.1, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.1 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.2 Distribution in Shares. Whenever the Company intends to make a distribution that consists of a dividend in, or free distribution of, Shares, the Company shall give

notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution, specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt of such notice from the Company, the Depositary shall establish the ADS Record Date upon the terms described in Section 4.9. Upon receipt of confirmation from the Custodian of the receipt of the Shares so distributed by the Company, the Depositary shall either (i) subject to Section 5.9, distribute to the Holders as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date, additional ADSs, which represent in the aggregate the number of Shares received as such dividend, or free distribution, subject to the other terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld), or (ii) if additional ADSs are not so distributed, take all actions necessary so that each ADS issued and outstanding after the ADS Record Date shall, to the extent permissible by law, thenceforth also represent rights and interests in the additional integral number of Shares distributed upon the Deposited Securities represented thereby (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes). In lieu of delivering fractional ADSs, the Depositary shall sell the number of Shares or ADSs, as the case may be, represented by the aggregate of such fractions and distribute the net proceeds upon the terms described in Section 4.1. In the event that the Depositary determines that any distribution in property (including Shares) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, or, if the Company in the fulfillment of its obligation under Section 5.7, has furnished an opinion of U.S. counsel determining that Shares must be registered under the Securities Act or other laws in order to be distributed to Holders (and no such registration statement has been declared effective), the Depositary may dispose of all or a portion of such property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable, and the Depositary shall distribute the net proceeds of any such sale (after deduction of (a) applicable taxes required to be withheld, and (b) fees and charges of, and expenses incurred by, the Depositary) to Holders entitled thereto upon the terms described in Section 4.1. The Depositary shall hold and/or distribute any unsold balance of such property in accordance with the provisions of the Deposit Agreement. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.2, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.2, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.2 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.3 Elective Distributions in Cash or Shares. Whenever the Company intends to make a distribution payable at the election of the holders of Deposited Securities in cash or in additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such elective distribution and whether or not it wishes such elective distribution to be made available to Holders of ADSs. Upon the timely

receipt of a notice indicating that the Company wishes such elective distribution to be made available to Holders of ADSs, the Depositary shall consult with the Company to determine, and the Company shall assist the Depositary in its determination, whether it is lawful and reasonably practicable to make such elective distribution available to the Holders of ADSs. The Depositary shall make such elective distribution available to Holders only if (i) the Company shall have timely requested that the elective distribution be made available to Holders, (ii) the Depositary shall have determined that such distribution is reasonably practicable and (iii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7. If the above conditions are not satisfied or if the Company requests such elective distribution not to be made available to Holders of ADSs, the Depositary shall establish the ADS Record Date on the terms described in Section 4.9 and, to the extent permitted by law, distribute to the Holders, on the basis of the same determination as is made in England and Wales in respect of the Shares for which no election is made, either (X) cash upon the terms described in Section 4.1 or (Y) additional ADSs representing such additional Shares upon the terms described in Section 4.2. If the above conditions are satisfied, the Depositary shall establish an ADS Record Date on the terms described in Section 4.9 and establish procedures to enable Holders to elect the receipt of the proposed distribution in cash or in additional ADSs. The Company shall assist the Depositary in establishing such procedures to the extent necessary. If a Holder elects to receive the proposed distribution (X) in cash, the distribution shall be made upon the terms described in Section 4.1, or (Y) in ADSs, the distribution shall be made upon the terms described in Section 4.2. Nothing herein shall obligate the Depositary to make available to Holders a method to receive the elective distribution in Shares (rather than ADSs). There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive elective distributions on the same terms and conditions as the holders of Shares. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.3, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.3, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.3 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.4 Distribution of Rights to Purchase Additional ADSs.

(a) **Distribution to ADS Holders.** Whenever the Company intends to distribute to the holders of the Deposited Securities rights to subscribe for additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution and whether or not it wishes such rights to be made available to Holders of ADSs. Upon the timely receipt of a notice indicating that the Company wishes such rights to be made available to Holders of ADSs, the Depositary shall consult with the Company to determine, and the Company shall assist the Depositary in its determination, whether it is lawful and reasonably practicable to make such rights available to the Holders. The Depositary shall make such rights available to Holders only if (i) the Company shall have timely requested that such rights be made available to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7, and (iii) the Depositary shall have determined that

such distribution of rights is reasonably practicable. In the event any of the conditions set forth above are not satisfied or if the Company requests that the rights not be made available to Holders of ADSs, the Depositary shall proceed with the sale of the rights as contemplated in Section 4.4(b) below. In the event all conditions set forth above are satisfied, the Depositary shall establish the ADS Record Date (upon the terms described in Section 4.9) and establish procedures to (x) distribute rights to purchase additional ADSs (by means of warrants or otherwise), (y) enable the Holders to exercise such rights (upon payment of the subscription price and of the applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes), and (z) deliver ADSs upon the valid exercise of such rights. The Company shall assist the Depositary to the extent necessary in establishing such procedures. Nothing herein shall obligate the Depositary to make available to the Holders a method to exercise rights to subscribe for Shares (rather than ADSs).

(b) **Sale of Rights.** If (i) the Company does not timely request the Depositary to make the rights available to Holders or requests that the rights not be made available to Holders, (ii) the Depositary fails to receive satisfactory documentation within the terms of Section 5.7, or determines it is not reasonably practicable to make the rights available to Holders, or (iii) any rights made available are not exercised and appear to be about to lapse, the Depositary shall determine whether it is lawful and reasonably practicable to sell such rights, in a riskless principal capacity, at such place and upon such terms (including public or private sale) as it may deem practicable. The Company shall assist the Depositary to the extent necessary to determine such legality and practicability. The Depositary shall, upon such sale, convert and distribute proceeds of such sale (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) upon the terms set forth in Section 4.1.

(c) **Lapse of Rights.** If the Depositary is unable to make any rights available to Holders upon the terms described in Section 4.4(a) or to arrange for the sale of the rights upon the terms described in Section 4.4(b), the Depositary shall allow such rights to lapse.

The Depositary shall not be liable for (i) any failure to accurately determine whether it may be lawful or practicable to make such rights available to Holders in general or any Holders in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or exercise, or (iii) the content of any materials forwarded to the Holders on behalf of the Company in connection with the rights distribution.

Notwithstanding anything to the contrary in this Section 4.4, if registration (under the Securities Act or any other applicable law) of the rights or the securities to which any rights relate may be required in order for the Company to offer such rights or such securities to Holders and to sell the securities represented by such rights, the Depositary will not distribute such rights to the Holders (i) unless and until a registration statement under the Securities Act (or other applicable law) covering such offering is in effect or (ii) unless the Company furnishes the Depositary opinion(s) of counsel for the Company in the United States and counsel to the Company in any other applicable country in which rights would be distributed, in each case satisfactory to the Depositary, to the effect that the offering and sale of such securities to Holders and Beneficial Owners are exempt from, or do not require registration under, the provisions of the Securities Act or any other applicable laws.

In the event that the Company, the Depositary or the Custodian shall be required to withhold and does withhold from any distribution of Deposited Property (including rights) an amount on account of taxes or other governmental charges, the amount distributed to the Holders of ADSs shall be reduced accordingly. In the event that the Depositary determines that any distribution of Deposited Property (including Shares and rights to subscribe therefor) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, the Depositary may dispose of all or a portion of such Deposited Property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable to pay any such taxes or charges.

There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive or exercise rights on the same terms and conditions as the holders of Shares or be able to exercise such rights. Nothing herein shall obligate the Company to file any registration statement in respect of any rights or Shares or other securities to be acquired upon the exercise of such rights.

Section 4.5 Distributions Other Than Cash, Shares or Rights to Purchase Shares.

(a) Whenever the Company intends to distribute to the holders of Deposited Securities property other than cash, Shares or rights to purchase additional Shares, the Company shall give timely notice thereof to the Depositary and shall indicate whether or not it wishes such distribution to be made to Holders of ADSs. Upon receipt of a notice indicating that the Company wishes such distribution to be made to Holders of ADSs, the Depositary shall consult with the Company, and the Company shall assist the Depositary, to determine whether such distribution to Holders is lawful and reasonably practicable. The Depositary shall not make such distribution unless (i) the Company shall have requested the Depositary to make such distribution to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7, and (iii) the Depositary shall have determined that such distribution is reasonably practicable.

(b) Upon receipt of satisfactory documentation and the request of the Company to distribute property to Holders of ADSs and after making the requisite determinations set forth in (a) above, the Depositary shall distribute the property so received to the Holders of record, as of the ADS Record Date, in proportion to the number of ADSs held by them respectively and in such manner as the Depositary may deem practicable for accomplishing such distribution (i) upon receipt of payment or net of the applicable fees and charges of, and expenses incurred by, the Depositary, and (ii) net of any applicable taxes required to be withheld. The Depositary may dispose of all or a portion of the property so distributed and deposited, in such amounts and in such manner (including public or private sale) as the Depositary may deem practicable or necessary to satisfy any taxes (including applicable interest and penalties) or other governmental charges applicable to the distribution.

(c) If (i) the Company does not request the Depositary to make such distribution to Holders or requests the Depositary not to make such distribution to Holders, (ii) the Depositary does not receive satisfactory documentation within the terms of Section 5.7, or (iii) the Depositary determines that all or a portion of such distribution is not reasonably practicable, the Depositary shall sell or cause such property to be sold in a public or private sale, at such place or places and

upon such terms as it may deem practicable and shall (i) cause the proceeds of such sale, if any, to be converted into Dollars and (ii) distribute the proceeds of such conversion received by the Depositary (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) to the Holders as of the ADS Record Date upon the terms of Section 4.1. If the Depositary is unable to sell such property, the Depositary may dispose of such property for the account of the Holders in any way it deems reasonably practicable under the circumstances.

(d) Neither the Depositary nor the Company shall be liable for (i) any failure to accurately determine whether it is lawful or practicable to make the property described in this Section 4.5 available to Holders in general or any Holders in particular, nor (ii) any loss incurred in connection with the sale or disposal of such property.

Section 4.6 Distributions with Respect to Deposited Securities in Bearer Form. Subject to the terms of this Article IV, distributions in respect of Deposited Securities that are held by the Depositary or the Custodian in bearer form shall be made to the Depositary for the account of the respective Holders of ADS(s) with respect to which any such distribution is made upon due presentation by the Depositary or the Custodian to the Company of any relevant coupons, talons, or certificates. The Company shall promptly notify the Depositary of such distributions. The Depositary or the Custodian shall promptly present such coupons, talons or certificates, as the case may be, in connection with any such distribution.

Section 4.7 Redemption. If the Company intends to exercise any right of redemption in respect of any of the Deposited Securities, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the intended date of redemption which notice shall set forth the particulars of the proposed redemption. Upon timely receipt of (i) such notice and (ii) satisfactory documentation given by the Company to the Depositary within the terms of Section 5.7, and only if, after consultation between the Depositary and the Company, the Depositary shall have determined that such proposed redemption is practicable, the Depositary shall provide to each Holder a notice setting forth the intended exercise by the Company of the redemption rights and any other particulars set forth in the Company's notice to the Depositary. The Depositary shall instruct the Custodian to present to the Company the Deposited Securities in respect of which redemption rights are being exercised against payment of the applicable redemption price. Upon receipt of confirmation from the Custodian that the redemption has taken place and that funds representing the redemption price have been received, the Depositary shall convert, transfer, and distribute the proceeds (net of applicable (a) fees and charges of, and the expenses incurred by, the Depositary, and (b) taxes), retire ADSs and cancel ADRs, if applicable, upon delivery of such ADSs by Holders thereof and the terms set forth in Sections 4.1 and 6.2. If less than all outstanding Deposited Securities are redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as may be determined by the Depositary after consultation with the Company. The redemption price per ADS shall be the dollar equivalent of the per share amount received by the Depositary (adjusted to reflect the ADS(s)-to-Share(s) ratio) upon the redemption of the Deposited Securities represented by ADSs (subject to the terms of Section 4.8 and the applicable fees and charges of, and expenses incurred by, the Depositary, and applicable taxes) multiplied by the number of Deposited Securities represented by each ADS redeemed.

Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed redemption provided for in this Section 4.7, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.7, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.7 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.8 Conversion of Foreign Currency. Whenever the Depositary or the Custodian shall receive Foreign Currency, by way of dividends or other distributions or the net proceeds from the sale of Deposited Property, which in the judgment of the Depositary can at such time be converted on a practicable basis, by sale or in any other manner that it may determine in accordance with applicable law, into Dollars transferable to the United States and distributable to the Holders entitled thereto, the Depositary shall convert or cause to be converted, by sale or in any other manner that it may determine, such Foreign Currency into Dollars, and shall distribute such Dollars (net of any applicable fees, taxes and any expenses incurred in connection with such conversion and distribution, including, without limitation, reasonable and customary fees, taxes and any expenses incurred in complying with currency exchange controls and other governmental requirements, transaction spreads, brokerage fees, transmission fees and expenses) in accordance with the terms of the applicable sections of the Deposit Agreement. If the Depositary shall have distributed warrants or other instruments that entitle the holders thereof to such Dollars, the Depositary shall distribute such Dollars to the holders of such warrants and/or instruments upon surrender thereof for cancellation, in either case without liability for interest thereon. Such distribution may be made upon an averaged or other practicable basis without regard to any distinctions among Holders on account of any application of exchange restrictions or otherwise.

If such conversion or distribution generally or with regard to a particular Holder can be effected only with the approval or license of any government or agency thereof, the Depositary shall have authority to file such application for approval or license, if any, as it may deem desirable. In no event, however, shall the Depositary be obligated to make such a filing.

If at any time the Depositary shall determine that in its judgment the conversion of any Foreign Currency and the transfer and distribution of proceeds of such conversion received by the Depositary is not practicable or lawful, or if any approval or license of any governmental authority or agency thereof that is required for such conversion, transfer and distribution is denied or, in the opinion of the Depositary, not obtainable at a reasonable cost or within a reasonable period, the Depositary may, in its reasonable discretion, (i) make such conversion and distribution in Dollars to the Holders for whom such conversion, transfer and distribution is lawful and practicable, (ii) distribute the Foreign Currency (or an appropriate document evidencing the right to receive such Foreign Currency) to Holders for whom this is lawful and practicable, or (iii) hold (or cause the Custodian to hold) such Foreign Currency (without liability for interest thereon) for the respective accounts of the Holders entitled to receive the same.

Section 4.9 Fixing of ADS Record Date. Whenever (a) the Depositary shall receive notice of the fixing of a record date by the Company for the determination of holders of Deposited Securities entitled to receive any distribution (whether in cash, Shares, rights, or other

distribution), (b) for any reason the Depositary causes a change in the number of Shares that are represented by each ADS, (c) the Depositary shall receive notice of any meeting of, or solicitation of consents or proxies of, holders of Shares or other Deposited Securities, or (d) the Depositary shall find it necessary or convenient in connection with the giving of any notice, solicitation of any consent or any other matter, the Depositary shall fix a record date (the "ADS Record Date") for the determination of the Holders of ADS(s) who shall be entitled to receive such distribution, to give instructions for the exercise of voting rights at any such meeting, to give or withhold such consent, to receive such notice or solicitation or to otherwise take action, or to exercise the rights of Holders with respect to such changed number of Shares represented by each ADS. The Depositary shall make reasonable efforts to establish the ADS Record Date as closely as practicable to the applicable record date for the Deposited Securities (if any) set by the Company in England and Wales and shall not announce the establishment of any ADS Record Date prior to the relevant corporate action having been made public by the Company (if such corporate action affects the Deposited Securities). Subject to applicable law and the provisions of Section 4.1 through 4.8 and to the other terms and conditions of the Deposit Agreement, only the Holders of ADSs at the close of business in New York on such ADS Record Date shall be entitled to receive such distribution, to give such voting instructions, to receive such notice or solicitation, or otherwise take action.

Section 4.10 Voting of Deposited Securities. As soon as practicable after receipt of notice of any meeting at which the holders of Deposited Securities are entitled to vote, or of solicitation of consents or proxies from holders of Deposited Securities, the Depositary shall fix the ADS Record Date in respect of such meeting or solicitation of consent or proxy in accordance with Section 4.9. The Depositary shall, if requested by the Company in writing in a timely manner (the Depositary having no obligation to take any further action if the request shall not have been received by the Depositary at least thirty (30) days prior to the date of such vote or meeting), at the Company's expense and provided no U.S. legal prohibitions exist, distribute as soon as practicable after receipt thereof to Holders as of the ADS Record Date: (a) such notice of meeting or solicitation of consent or proxy, (b) a statement that the Holders at the close of business on the ADS Record Date will be entitled, subject to any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of or governing the Deposited Securities (which provisions, if any, shall be summarized in pertinent part by the Company), to instruct the Depositary as to the exercise of the voting rights, if any, pertaining to the Deposited Securities represented by such Holder's ADSs, and (c) a brief statement as to the manner and timing (such timing to be determined after consultation with the Company) in which such voting instructions may be given to the Depositary or in which voting instructions may be deemed to have been given in accordance with this Section 4.10 if no instructions are received prior to the deadline set for such purposes to the Depositary to give a discretionary proxy to a person designated by the Company. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to timely request that the Depositary distribute the information as provided for in this Section 4.10, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.10, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.10 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Notwithstanding anything contained in the Deposit Agreement or any ADR, with the Company's prior written consent, the Depositary may, to the extent not prohibited by law or regulations, or by the requirements of any stock exchange on which the ADSs may be listed, in lieu of distribution of the materials provided to the Depositary in connection with any meeting of, or solicitation of consents or proxies from, holders of Deposited Securities, distribute to the Holders a notice that provides Holders with, or otherwise publicize to Holders, instructions on how to retrieve such materials or receive such materials upon request (*e.g.*, by reference to a website containing the materials for retrieval or a contact for requesting copies of the materials).

The Depositary has been advised by the Company that the Articles of Association (as in effect on the date hereof), provide that voting at any meeting of shareholders is by show of hands unless a poll is demanded. The Depositary will not join in demanding a poll, whether or not requested to do so by Holders of ADSs. Under the Articles of Association (as in effect on the date hereof), a poll may be demanded by (i) the chairman of the general meeting; (ii) by at least two members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting; (iii) by any member of members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting and/or one tenth of the aggregate sum of the total sum paid up on all shares of the Company; or (iv) by any member or members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

Voting instructions may be given only in respect of a number of ADSs representing an integral number of Deposited Securities. Upon the timely receipt from a Holder of ADSs as of the ADS Record Date of voting instructions in the manner specified by the Depositary, the Depositary shall endeavor, insofar as practicable and permitted under any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of the Deposited Securities, to vote, or cause the Custodian to vote, the Deposited Securities (in person or by proxy) represented by such Holder's ADSs as follows: (i) in the event voting takes place at a shareholders' meeting by show of hands, the Depositary will instruct the Custodian to vote all Deposited Securities in accordance with the voting instructions received from a majority of Holders of ADSs who provided voting instructions and (ii) in the event voting takes place at a shareholders' meeting by poll, the Depositary will instruct the Custodian to vote the Deposited Securities in accordance with the voting instructions received from the Holders of ADSs. If the Depositary does not receive voting instructions from a Holder as of the ADS Record Date on or before the date established by the Depositary for such purpose, such Holder shall be deemed, and the Depositary shall deem such Holder, to have instructed the Depositary to give a discretionary proxy to a person designated by the Company to vote the Deposited Securities; provided, however, that no such discretionary proxy shall be given by the Depositary with respect to any matter to be voted upon as to which the Company informs the Depositary that (a) the Company does not wish such proxy to be given, (b) substantial opposition exists, or (c) the rights of holders of Deposited Securities may be adversely affected.

Deposited Securities represented by ADSs for which no timely voting instructions are received by the Depositary from the Holder shall not be voted (except as contemplated in this Section 4.10). Neither the Depositary nor the Custodian shall under any circumstances exercise any discretion as to voting and neither the Depositary nor the Custodian shall vote, attempt to exercise the right to vote, or in any way make use of, for purposes of establishing a quorum or otherwise, the Deposited Securities represented by ADSs, except pursuant to and in accordance with the voting instructions timely received from Holders or as otherwise contemplated herein. If the Depositary timely receives voting instructions from a Holder which fail to specify the manner in which the Depositary is to vote the Deposited Securities represented by such Holder's ADSs, the Depositary will deem such Holder (unless otherwise specified in the notice distributed to Holders) to have instructed the Depositary to vote in favor of the items set forth in such voting instructions.

Notwithstanding anything else contained herein, the Depositary shall, if so requested in writing by the Company, represent all Deposited Securities (whether or not voting instructions have been received in respect of such Deposited Securities from Holders as of the ADS Record Date) for the sole purpose of establishing quorum at a meeting of shareholders.

Notwithstanding anything else contained in the Deposit Agreement or any ADR, the Depositary shall not have any obligation to take any action with respect to any meeting, or solicitation of consents or proxies, of holders of Deposited Securities if the taking of such action would violate U.S. or English laws. The Company agrees to take any and all actions reasonably necessary and as permitted by the laws of England and Wales to enable Holders and Beneficial Owners to exercise the voting rights accruing to the Deposited Securities and to deliver to the Depositary an opinion of U.S. counsel addressing any actions requested to be taken if so reasonably requested by the Depositary.

There can be no assurance that Holders generally or any Holder in particular will receive the notice described above with sufficient time to enable the Holder to return voting instructions to the Depositary in a timely manner.

Section 4.11 **Changes Affecting Deposited Securities.** Upon any change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of Deposited Securities, or upon any recapitalization, reorganization, merger, consolidation or sale of assets affecting the Company or to which it is a party, any property which shall be received by the Depositary or the Custodian in exchange for, or in conversion of, or replacement of, or otherwise in respect of, such Deposited Securities shall, to the extent permitted by law, be treated as new Deposited Property under the Deposit Agreement, and the ADSs shall, subject to the provisions of the Deposit Agreement, any ADR(s) evidencing such ADSs and applicable law, represent the right to receive such additional or replacement Deposited Property. In giving effect to such change, split-up, cancellation, consolidation or other reclassification of Deposited Securities, recapitalization, reorganization, merger, consolidation or sale of assets, the Depositary may, with the Company's approval, and shall, if the Company shall so request, subject to the terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes) and receipt of an opinion of counsel to the Company satisfactory to the Depositary that such actions are not in violation of any

applicable laws or regulations, (i) issue and deliver additional ADSs as in the case of a stock dividend on the Shares, (ii) amend the Deposit Agreement and the applicable ADRs, (iii) amend the applicable Registration Statement(s) on Form F-6 as filed with the Commission in respect of the ADSs, (iv) call for the surrender of outstanding ADRs to be exchanged for new ADRs, and (v) take such other actions as are appropriate to reflect the transaction with respect to the ADSs. The Company agrees to, jointly with the Depositary, amend the Registration Statement on Form F-6 as filed with the Commission to permit the issuance of such new form of ADRs. Notwithstanding the foregoing, in the event that any Deposited Property so received may not be lawfully distributed to some or all Holders, the Depositary may, with the Company's approval, and shall, if the Company requests, subject to receipt of an opinion of Company's counsel satisfactory to the Depositary that such action is not in violation of any applicable laws or regulations, sell such Deposited Property at public or private sale, at such place or places and upon such terms as it may deem proper and may allocate the net proceeds of such sales (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) for the account of the Holders otherwise entitled to such Deposited Property upon an averaged or other practicable basis without regard to any distinctions among such Holders and distribute the net proceeds so allocated to the extent practicable as in the case of a distribution received in cash pursuant to Section 4.1. The Depositary shall not be responsible for (i) any failure to determine that it may be lawful or practicable to make such Deposited Property available to Holders in general or to any Holder in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or (iii) any liability to the purchaser of such Deposited Property.

Section 4.12 Available Information. The Company is subject to the periodic reporting requirements of the Exchange Act and, accordingly, is required to file or furnish certain reports with the Commission. These reports can be retrieved from the Commission's website (www.sec.gov) and can be inspected and copied at the public reference facilities maintained by the Commission located (as of the date of the Deposit Agreement) at 100 F Street, N.E., Washington D.C. 20549.

Section 4.13 Reports. The Depositary shall make available for inspection by Holders at its Principal Office, as promptly as practicable after receipt thereof, any reports and communications, including any proxy soliciting materials, received from the Company which are both (a) received by the Depositary, the Custodian, or the nominee of either of them as the holder of the Deposited Property and (b) made generally available to the holders of such Deposited Property by the Company. The Depositary shall also provide or make available to Holders copies of such reports when furnished by the Company pursuant to Section 5.6.

Section 4.14 List of Holders. Promptly upon written request by the Company, the Depositary shall furnish to it a list, as of a recent date, of the names, addresses and holdings of ADSs of all Holders.

Section 4.15 Taxation. The Depositary will, and will instruct the Custodian to, forward to the Company or its agents such information from its records as the Company may reasonably request to enable the Company or its agents to file the necessary tax reports with governmental authorities or agencies. The Depositary, the Custodian or the Company and its agents may file such reports as are necessary to reduce or eliminate applicable taxes on dividends and on other

distributions in respect of Deposited Property under applicable tax treaties or laws for the Holders and Beneficial Owners. In accordance with instructions from the Company and to the extent practicable, the Depositary or the Custodian will take reasonable administrative actions to obtain tax refunds, reduced withholding of tax at source on dividends and other benefits under applicable tax treaties or laws with respect to dividends and other distributions on the Deposited Property. As a condition to receiving such benefits, Holders and Beneficial Owners of ADSs may be required from time to time, and in a timely manner, to file such proof of taxpayer status, residence and beneficial ownership (as applicable), to execute such certificates and to make such representations and warranties, or to provide any other information or documents, as the Depositary or the Custodian may deem necessary or proper to fulfill the Depositary's or the Custodian's obligations under applicable law. The Depositary and the Company shall have no obligation or liability to any person if any Holder or Beneficial Owner fails to provide such information or if such information does not reach the relevant tax authorities in time for any Holder or Beneficial Owner to obtain the benefits of any tax treatment. The Holders and Beneficial Owners shall indemnify the Depositary, the Company, the Custodian and any of their respective directors, employees, agents and Affiliates against, and hold each of them harmless from, any claims by any governmental authority with respect to taxes, additions to tax, penalties or interest arising out of any refund of taxes, reduced rate of withholding at source or other tax benefit obtained for that Holder or Beneficial Owner which is required to be paid to such governmental authority.

If the Company (or any of its agents) withholds from any distribution any amount on account of taxes or governmental charges, or pays any other tax in respect of such distribution (*e.g.*, stamp duty tax, capital gains or other similar tax), the Company shall use its commercially reasonable efforts to (and shall cause such agent to) forward promptly to the Depositary information about such taxes or governmental charges withheld or paid, and, if so requested, the tax receipt (or other proof of payment to the applicable governmental authority) therefor, in each case, in a form satisfactory to the Depositary. The Depositary shall, to the extent required by U.S. law, report to Holders any taxes withheld by it or the Custodian, and, if such information is provided to it by the Company, any taxes withheld by the Company. The Depositary and the Custodian shall not be required to provide the Holders with any evidence of the remittance by the Company (or its agents) of any taxes withheld, or of the payment of taxes by the Company, except to the extent the evidence is provided by the Company to the Depositary or the Custodian, as applicable. Neither the Depositary nor the Custodian shall be liable for the failure by any Holder or Beneficial Owner to obtain the benefits of credits on the basis of non-U.S. tax paid against such Holder's or Beneficial Owner's income tax liability.

The Depositary is under no obligation to provide the Holders and Beneficial Owners with any information about the tax status of the Company except to the extent that the Company provides such information to the Depositary for distribution to the Holders and Beneficial Owners. The Depositary shall not incur any liability for any tax consequences that may be incurred by Holders and Beneficial Owners on account of their ownership of the ADSs, including without limitation, tax consequences resulting from the Company (or any of its subsidiaries) being treated as a "Passive Foreign Investment Company" (in each case as defined in the U.S. Internal Revenue Code and the regulations issued thereunder) or otherwise.

ARTICLE V

THE DEPOSITARY, THE CUSTODIAN AND THE COMPANY

Section 5.1 Maintenance of Office and Transfer Books by the Registrar. Until termination of the Deposit Agreement in accordance with its terms, the Registrar shall maintain in the Borough of Manhattan, the City of New York, an office and facilities for the issuance and delivery of ADSs, the acceptance for surrender of ADS(s) for the purpose of withdrawal of Deposited Securities, the registration of issuances, cancellations, transfers, combinations and split-ups of ADS(s) and, if applicable, to countersign ADRs evidencing the ADSs so issued, transferred, combined or split-up, in each case in accordance with the provisions of the Deposit Agreement.

The Registrar shall keep books for the registration of ADSs which at all reasonable times shall be open for inspection by the Company and by the Holders of such ADSs, provided that such inspection shall not be, to the Registrar's knowledge, for the purpose of communicating with Holders of such ADSs in the interest of a business or object other than the business of the Company or other than a matter related to the Deposit Agreement or the ADSs.

The Registrar may close the transfer books with respect to the ADSs, at any time or from time to time, when deemed necessary or advisable by it in good faith in connection with the performance of its duties hereunder, or at the reasonable written request of the Company subject, in all cases, to Section 7.8(a).

If any ADSs are listed on one or more stock exchanges or automated quotation systems in the United States, the Depositary shall act as Registrar or, with written notice given as promptly as practicable to the Company, appoint a Registrar or one or more co-registrars for registration of issuances, cancellations, transfers, combinations and split-ups of ADSs and, if applicable, to countersign ADRs evidencing the ADSs so issued, transferred, combined or split-up, in accordance with any requirements of such exchanges or systems. Such Registrar or co-registrars may be removed and a substitute or substitutes appointed by the Depositary, upon written notice given as promptly as practicable to the Company.

Section 5.2 Exoneration. Notwithstanding anything contained in the Deposit Agreement or any ADR, neither the Depositary nor the Company shall be obligated to do or perform any act which is inconsistent with the provisions of the Deposit Agreement or incur any liability (to the extent not limited by Section 7.8(b)) (i) if the Depositary, the Custodian, the Company or their respective agents shall be prevented or forbidden from, or delayed in, doing or performing any act or thing required or contemplated by the terms of the Deposit Agreement, by reason of any provision of any present or future law or regulation of the United States, England and Wales or any other country, or of any other governmental authority or regulatory authority or stock exchange, or on account of potential criminal or civil penalties or restraint, or by reason of any provision, present or future, of the Articles of Association of the Company or any provision of or governing any Deposited Securities, or by reason of any act of God or war or other circumstances beyond its control (including, without limitation, nationalization, expropriation, currency restrictions, work stoppage, strikes, civil unrest, acts of terrorism, revolutions, rebellions,

explosions and computer failure), (ii) by reason of any exercise of, or failure to exercise, any discretion provided for in the Deposit Agreement or in the Articles of Association of the Company or provisions of or governing Deposited Securities, (iii) for any action or inaction in reliance upon the advice of or information from legal counsel, accountants, any person presenting Shares for deposit, any Holder, any Beneficial Owner or authorized representative thereof, or any other person believed by it in good faith to be competent to give such advice or information, (iv) for the inability by a Holder or Beneficial Owner to benefit from any distribution, offering, right or other benefit which is made available to holders of Deposited Securities but is not, under the terms of the Deposit Agreement, made available to Holders of ADSs, (v) for any action or inaction of any clearing or settlement system (and any participant thereof) for the Deposited Property or the ADSs, or (vi) for any consequential or punitive damages (including lost profits) for any breach of the terms of the Deposit Agreement.

The Depositary, its controlling persons, its agents, any Custodian and the Company, its controlling persons and its agents may rely and shall be protected in acting upon any written notice, request or other document believed by it to be genuine and to have been signed or presented by the proper party or parties.

Section 5.3 Standard of Care. The Company and the Depositary assume no obligation and shall not be subject to any liability under the Deposit Agreement or any ADRs to any Holder(s) or Beneficial Owner(s), except that the Company and the Depositary agree to perform their respective obligations specifically set forth in the Deposit Agreement or the applicable ADRs without negligence or bad faith.

Without limitation of the foregoing, neither the Depositary, nor the Company, nor any of their respective controlling persons, or agents, shall be under any obligation to appear in, prosecute or defend any action, suit or other proceeding in respect of any Deposited Property or in respect of the ADSs, which in its opinion may involve it in expense or liability, unless indemnity satisfactory to it against all expense (including fees and disbursements of counsel) and liability be furnished as often as may be required (and no Custodian shall be under any obligation whatsoever with respect to such proceedings, the responsibility of the Custodian being solely to the Depositary).

The Depositary and its agents shall not be liable for any failure to carry out any instructions to vote any of the Deposited Securities, or for the manner in which any vote is cast or the effect of any vote, provided that any such action or omission is in good faith and without negligence and in accordance with the terms of the Deposit Agreement. The Depositary shall not incur any liability for any failure to accurately determine that any distribution or action may be lawful or reasonably practicable, for the content of any information submitted to it by the Company for distribution to the Holders or for any inaccuracy of any translation thereof, for any investment risk associated with acquiring an interest in the Deposited Property, for the validity or worth of the Deposited Property, for the value of any Deposited Property or any distribution thereon, for any interest on Deposited Property, for any tax consequences that may result from the ownership of ADSs, Shares or other Deposited Property, for the credit-worthiness of any third party, for allowing any rights to lapse upon the terms of the Deposit Agreement, for the failure or timeliness of any notice from the Company, or for any action of or failure to act by, or any information provided or not provided by, DTC or any DTC Participant.

The Depositary shall not be liable for any acts or omissions made by a successor depositary whether in connection with a previous act or omission of the Depositary or in connection with any matter arising wholly after the removal or resignation of the Depositary, provided that in connection with the issue out of which such potential liability arises the Depositary performed its obligations without negligence or bad faith while it acted as Depositary for the Company.

Section 5.4 Resignation and Removal of the Depositary; Appointment of Successor Depositary. The Depositary may at any time resign as Depositary hereunder by written notice of resignation delivered to the Company, such resignation to be effective on the earlier of (i) the 90th day after delivery thereof to the Company (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2), or (ii) the appointment by the Company of a successor depositary and its acceptance of such appointment as hereinafter provided.

The Depositary may at any time be removed by the Company by written notice of such removal, which removal shall be effective on the later of (i) the 90th day after delivery thereof to the Depositary (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2), or (ii) upon the appointment by the Company of a successor depositary and its acceptance of such appointment as hereinafter provided.

In case at any time the Depositary acting hereunder shall resign or be removed, the Company shall use its best efforts to appoint a successor depositary, which shall be a bank or trust company having an office in the Borough of Manhattan, the City of New York. Every successor depositary shall be required by the Company to execute and deliver to its predecessor and to the Company an instrument in writing accepting its appointment hereunder, and thereupon such successor depositary, without any further act or deed (except as required by applicable law), shall become fully vested with all the rights, powers, duties and obligations of its predecessor (other than as contemplated in Sections 5.8 and 5.9). The predecessor depositary, upon payment of all sums due it and on the written request of the Company, shall, (i) execute and deliver an instrument transferring to such successor all rights and powers of such predecessor hereunder (other than as contemplated in Sections 5.8 and 5.9), (ii) duly assign, transfer and deliver all of the Depositary's right, title and interest to the Deposited Property to such successor, and (iii) deliver to such successor a list of the Holders of all outstanding ADSs and such other information relating to ADSs and Holders thereof as the successor may reasonably request. Any such successor depositary shall promptly provide notice of its appointment to such Holders.

Any entity into or with which the Depositary may be merged or consolidated shall be the successor of the Depositary without the execution or filing of any document or any further act.

Section 5.5 The Custodian. The Depositary has initially appointed Citibank, N.A. (London) as Custodian for the purpose of the Deposit Agreement. The Custodian or its successors in acting hereunder shall be subject at all times and in all respects to the direction of the Depositary for the Deposited Property for which the Custodian acts as custodian and shall be responsible solely to it. If any Custodian resigns or is discharged from its duties hereunder with respect to any Deposited Property and no other Custodian has previously been appointed hereunder, the Depositary shall promptly appoint a substitute custodian. The Depositary shall require such resigning or discharged Custodian to Deliver, or cause the Delivery of, the Deposited Property

held by it, together with all such records maintained by it as Custodian with respect to such Deposited Property as the Depositary may request, to the Custodian designated by the Depositary. Whenever the Depositary determines, in its discretion, that it is appropriate to do so, it may appoint an additional custodian with respect to any Deposited Property, or discharge the Custodian with respect to any Deposited Property and appoint a substitute custodian, which shall thereafter be Custodian hereunder with respect to the Deposited Property. Immediately upon any such change, the Depositary shall give notice thereof in writing to all Holders of ADSs, each other Custodian and the Company.

Citibank, N.A. may at any time act as Custodian of the Deposited Property pursuant to the Deposit Agreement, in which case any reference to Custodian shall mean Citibank, N.A. solely in its capacity as Custodian pursuant to the Deposit Agreement and the Depositary shall promptly give notice thereof to the Company. Notwithstanding anything contained in the Deposit Agreement or any ADR, the Depositary shall not be obligated to give notice to any Holders of ADSs or any other Custodian of its acting as Custodian pursuant to the Deposit Agreement.

Upon the appointment of any successor depositary, any Custodian then acting hereunder shall, unless otherwise instructed by the Depositary, continue to be the Custodian of the Deposited Property without any further act or writing, and shall be subject to the direction of the successor depositary. The successor depositary so appointed shall, nevertheless, on the written request of any Custodian, execute and deliver to such Custodian all such instruments as may be proper to give to such Custodian full and complete power and authority to act on the direction of such successor depositary.

Section 5.6 Notices and Reports. On or before the first date on which the Company gives notice, by publication or otherwise, of any meeting of holders of Shares or other Deposited Securities, or of any adjourned meeting of such holders, or of the taking of any action by such holders other than at a meeting, or of the taking of any action in respect of any cash or other distributions or the offering of any rights in respect of Deposited Securities, the Company shall transmit to the Depositary and the Custodian a copy of the notice thereof in the English language but otherwise in the form given or to be given to holders of Shares or other Deposited Securities. The Company shall also furnish to the Custodian and the Depositary a summary, in English, of any applicable provisions or proposed provisions of the Articles of Association of the Company that may be relevant or pertain to such notice of meeting or be the subject of a vote thereat.

The Company will also transmit to the Depositary (a) an English language version of the other notices, reports and communications which are made generally available by the Company to holders of its Shares or other Deposited Securities and (b) the English-language versions of the Company's annual and semi-annual reports prepared in accordance with the applicable requirements of the Commission. The Depositary shall arrange, at the request of the Company and at the Company's expense, to provide copies thereof to all Holders or make such notices, reports and other communications available to all Holders on a basis similar to that for holders of Shares or other Deposited Securities or on such other basis as the Company may advise the Depositary or as may be required by any applicable law, regulation or stock exchange requirement. The Company has delivered to the Depositary and the Custodian a copy of the Company's Articles of Association along with the provisions of or governing the Shares and any other Deposited

Securities issued by the Company in connection with such Shares, and promptly upon any amendment thereto or change therein, the Company shall deliver to the Depositary and the Custodian a copy of such amendment thereto or change therein to the extent such amendment or change is not available on the Company's website or is not otherwise publicly available. The Depositary may rely upon such copy for all purposes of the Deposit Agreement.

The Depositary will, at the expense of the Company, make available a copy of any such notices, reports or communications issued by the Company and delivered to the Depositary for inspection by the Holders of the ADSs at the Depositary's Principal Office, at the office of the Custodian and at any other designated transfer office.

Section 5.7 Issuance of Additional Shares, ADSs etc. The Company agrees that in the event it or any of its Affiliates proposes (i) an issuance, sale or distribution of additional Shares, (ii) an offering of rights to subscribe for Shares or other Deposited Securities, (iii) an issuance or assumption of securities convertible into or exchangeable for Shares, (iv) an issuance of rights to subscribe for securities convertible into or exchangeable for Shares, (v) an elective dividend of cash or Shares, (vi) a redemption of Deposited Securities, (vii) a meeting of holders of Deposited Securities, or solicitation of consents or proxies, relating to any reclassification of securities, merger or consolidation or transfer of assets, (viii) any assumption, reclassification, recapitalization, reorganization, merger, consolidation or sale of assets which affects the Deposited Securities, or (ix) a distribution of securities other than Shares, it will obtain U.S. legal advice and take all steps necessary to ensure that the application of the proposed transaction to Holders and Beneficial Owners does not violate the registration provisions of the Securities Act, or any other applicable laws (including, without limitation, the Investment Company Act of 1940, as amended, the Exchange Act and the securities laws of the states of the U.S.). In support of the foregoing, the Company will furnish to the Depositary (a) a written opinion of U.S. counsel (reasonably satisfactory to the Depositary) stating whether such transaction (1) requires a registration statement under the Securities Act to be in effect or (2) is exempt from the registration requirements of the Securities Act and (b) an opinion of English counsel stating that (1) making the transaction available to Holders and Beneficial Owners does not violate the laws or regulations of England and Wales and (2) all requisite regulatory consents and approvals have been obtained in England and Wales. If the filing of a registration statement is required, the Depositary shall not have any obligation to proceed with the transaction unless it shall have received evidence reasonably satisfactory to it that such registration statement has been declared effective. If, being advised by counsel, the Company determines that a transaction is required to be registered under the Securities Act, the Company will either (i) register such transaction to the extent necessary, (ii) alter the terms of the transaction to avoid the registration requirements of the Securities Act or (iii) direct the Depositary to take specific measures, in each case as contemplated in the Deposit Agreement, to prevent such transaction from violating the registration requirements of the Securities Act. The Company agrees with the Depositary that neither the Company nor any of its Affiliates will at any time (i) deposit any Shares or other Deposited Securities, either upon original issuance or upon a sale of Shares or other Deposited Securities previously issued and reacquired by the Company or by any such Affiliate, or (ii) issue additional Shares, rights to subscribe for such Shares, securities convertible into or exchangeable for Shares or rights to subscribe for such securities or distribute securities other than Shares, unless such transaction and the securities issuable in such transaction do not violate the registration provisions of the Securities Act, or any other applicable laws (including, without limitation, the Investment Company Act of 1940, as amended, the Exchange Act and the securities laws of the states of the U.S.).

Notwithstanding anything else contained in the Deposit Agreement, nothing in the Deposit Agreement shall be deemed to obligate the Company to file any registration statement in respect of any proposed transaction.

Section 5.8 Indemnification. The Depositary agrees to indemnify the Company and its directors, officers, employees, agents and Affiliates against, and hold each of them harmless from, any direct loss, liability, tax, charge or expense of any kind whatsoever (including, but not limited to, the reasonable fees and expenses of counsel) which may arise out of acts performed or omitted by the Depositary under the terms hereof due to the negligence or bad faith of the Depositary.

The Company agrees to indemnify the Depositary, the Custodian and any of their respective directors, officers, employees, agents and Affiliates against, and hold each of them harmless from, any direct loss, liability, tax, charge or expense of any kind whatsoever (including, but not limited to, the reasonable fees and expenses of counsel) that may arise (a) out of, or in connection with, any offer, issuance, sale, resale, transfer, deposit or withdrawal of ADRs, ADSs, the Shares, or other Deposited Securities, as the case may be, to the extent it is not unlawful for the Company to indemnify such person at such time under applicable English law, (b) out of, or as a result of, any offering documents in respect thereof or (c) out of acts performed or omitted, including, but not limited to, any delivery by the Depositary on behalf of the Company of information regarding the Company, in connection with the Deposit Agreement, any ancillary or supplemental agreement entered into between the Company and the Depositary, the ADRs, the ADSs, the Shares, or any Deposited Property, in any such case (i) by the Depositary, the Custodian or any of their respective directors, officers, employees, agents and Affiliates, except to the extent such loss, liability, tax, charge or expense is due to the fraud, negligence or bad faith of any of them, or (ii) by the Company or any of its directors, officers, employees, agents and Affiliates; provided, however, that the Company shall not be liable for any fees, charges or expenses payable by third party Holders or Beneficial Owners under this Deposit Agreement. The Company shall not indemnify the Depositary or the Custodian (for so long as the Custodian is a branch of Citibank, N.A.) against any liability or expense arising out of information relating to the Depositary or such Custodian, as the case may be, furnished in a signed writing to the Company, executed by the Depositary expressly for use in any registration statement, prospectus or preliminary prospectus relating to any Deposited Securities represented by the ADSs.

The obligations set forth in this Section shall survive the termination of the Deposit Agreement and the succession or substitution of any party hereto.

Any person seeking indemnification hereunder (an “indemnified person”) shall notify the person from whom it is seeking indemnification (the “indemnifying person”) of the commencement of any indemnifiable action or claim promptly after such indemnified person becomes aware of such commencement (provided that the failure to make such notification shall not affect such indemnified person’s rights to seek indemnification except to the extent the indemnifying person is materially prejudiced by such failure) and shall consult in good faith with the indemnifying person as to the conduct of the defense of such action or claim that may give rise

to an indemnity hereunder, which defense shall be reasonable in the circumstances. No indemnified person shall compromise or settle any action or claim that may give rise to an indemnity hereunder without the consent of the indemnifying person, which consent shall not be unreasonably withheld.

Section 5.9 ADS Fees and Charges. The Company, the Holders, the Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with the issuance and cancellation of ADSs, and persons receiving ADSs upon issuance or for whom ADSs are being cancelled shall be required to pay the ADS fees and charges identified as payable by them respectively in the ADS fee schedule attached hereto as Exhibit B. All ADS fees and charges so payable may be deducted from distributions or must be remitted to the Depositary, or its designee, may, at any time and from time to time, be changed by agreement between the Depositary and the Company, but, in the case of ADS fees and charges payable by Holders and Beneficial Owners, only in the manner contemplated in Section 6.1. The Depositary shall provide, without charge, a copy of its latest ADS fee schedule to anyone upon request.

ADS fees and charges payable upon (i) the issuance of ADSs and (ii) the cancellation of ADSs will be payable by the person for whom the ADSs are so issued by the Depositary (in the case of ADS issuances) and by the person for whom ADSs are being cancelled by the Depositary (in the case of ADS cancellations). In the case of ADSs issued by the Depositary into DTC or presented to the Depositary via DTC, the ADS issuance and cancellation fees and charges will be payable by the DTC Participant(s) receiving the ADSs from the Depositary or the DTC Participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the Beneficial Owner(s) and will be charged by the DTC Participant(s) to the account(s) of the applicable Beneficial Owner(s) in accordance with the procedures and practices of the DTC Participant(s) as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are payable by Holders as of the applicable ADS Record Date established by the Depositary. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, the applicable Holders as of the ADS Record Date established by the Depositary will be invoiced for the amount of the ADS fees and charges and such ADS fees may be deducted from distributions made to Holders. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC Participants in accordance with the procedures and practices prescribed by DTC from time to time and the DTC Participants in turn charge the amount of such ADS fees and charges to the Beneficial Owners for whom they hold ADSs.

The Depositary may reimburse the Company for certain expenses incurred by the Company in respect of the ADR program established pursuant to the Deposit Agreement, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as the Company and the Depositary agree from time to time. The Company shall pay to the Depositary such fees and charges, and reimburse the Depositary for such out-of-pocket expenses, as the Depositary and the Company may agree from time to time. Responsibility for payment of such fees, charges and reimbursements may from time to time be changed by agreement between the Company and the Depositary. Unless otherwise agreed, the Depositary shall present its statement for such fees, charges and reimbursements to the Company once every three months. The charges and expenses of the Custodian are for the sole account of the Depositary.

The obligations of Holders and Beneficial Owners to pay ADS fees and charges shall survive the termination of the Deposit Agreement. As to any Depositary, upon the resignation or removal of such Depositary as described in Section 5.4, the right to collect ADS fees and charges shall extend for those ADS fees and charges incurred prior to the effectiveness of such resignation or removal.

Section 5.10 Restricted Securities Owners. The Company agrees to advise in writing each of the persons or entities who, to the knowledge of the Company, holds Restricted Securities that such Restricted Securities are ineligible for deposit hereunder (except under the circumstances contemplated in Section 2.14) and, to the extent practicable, shall require each of such persons to represent in writing that such person will not deposit Restricted Securities hereunder (except under the circumstances contemplated in Section 2.14).

ARTICLE VI

AMENDMENT AND TERMINATION

Section 6.1 Amendment/Supplement. Subject to the terms and conditions of this Section 6.1 and applicable law, the ADRs outstanding at any time, the provisions of the Deposit Agreement and the form of ADR attached hereto and to be issued under the terms hereof may at any time and from time to time be amended or supplemented by written agreement between the Company and the Depositary in any respect which they may deem necessary or desirable without the prior written consent of the Holders or Beneficial Owners. Any amendment or supplement which shall impose or increase any fees or charges (other than charges in connection with foreign exchange control regulations, and taxes and other governmental charges, delivery and other such expenses), or which shall otherwise materially prejudice any substantial existing right of Holders or Beneficial Owners, shall not, however, become effective as to outstanding ADSs until the expiration of thirty (30) days after notice of such amendment or supplement shall have been given to the Holders of outstanding ADSs. Notice of any amendment to the Deposit Agreement or any ADR shall not need to describe in detail the specific amendments effectuated thereby, and failure to describe the specific amendments in any such notice shall not render such notice invalid, provided, however, that, in each such case, the notice given to the Holders identifies a means for Holders and Beneficial Owners to retrieve or receive the text of such amendment (*e.g.*, upon retrieval from the Commission's, the Depositary's or the Company's website or upon request from the Depositary). The parties hereto agree that any amendments or supplements which (i) are reasonably necessary (as agreed by the Company and the Depositary) in order for (a) the ADSs to be registered on Form F-6 under the Securities Act or (b) the ADSs to be settled solely in electronic book-entry form and (ii) do not in either such case impose or increase any fees or charges to be borne by Holders, shall be deemed not to materially prejudice any substantial rights of Holders or Beneficial Owners. Every Holder and Beneficial Owner at the time any amendment or supplement so becomes effective shall be deemed, by continuing to hold such ADSs, to consent and agree to such amendment or supplement and to be bound by the Deposit Agreement and the ADR, if applicable, as amended or supplemented thereby. In no event shall any amendment or supplement

impair the right of the Holder to surrender such ADS and receive therefor the Deposited Securities represented thereby, except in order to comply with mandatory provisions of applicable law. Notwithstanding the foregoing, if any governmental body should adopt new laws, rules or regulations which would require an amendment of, or supplement to, the Deposit Agreement to ensure compliance therewith, the Company and the Depositary may amend or supplement the Deposit Agreement and any ADRs at any time in accordance with such changed laws, rules or regulations. Such amendment or supplement to the Deposit Agreement and any ADRs in such circumstances may become effective before a notice of such amendment or supplement is given to Holders or within any other period of time as required for compliance with such laws, rules or regulations.

Section 6.2 Termination. The Depositary shall, at any time at the written direction of the Company, terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. If ninety (90) days shall have expired after (i) the Depositary shall have delivered to the Company a written notice of its election to resign, or (ii) the Company shall have delivered to the Depositary a written notice of the removal of the Depositary, and, in either case, a successor depositary shall not have been appointed and accepted its appointment as provided in Section 5.4 of the Deposit Agreement, the Depositary may terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. The date so fixed for termination of the Deposit Agreement in any termination notice so distributed by the Depositary to the Holders of ADSs is referred to as the "Termination Date". Until the Termination Date, the Depositary shall continue to perform all of its obligations under the Deposit Agreement, and the Holders and Beneficial Owners will be entitled to all of their rights under the Deposit Agreement.

If any ADSs shall remain outstanding after the Termination Date, the Registrar and the Depositary shall not, after the Termination Date, have any obligation to perform any further acts under the Deposit Agreement, except that the Depositary shall, subject, in each case, to the terms and conditions of the Deposit Agreement, continue to (i) collect dividends and other distributions pertaining to Deposited Securities, (ii) sell Deposited Property received in respect of Deposited Securities, (iii) deliver Deposited Securities, together with any dividends or other distributions received with respect thereto and the net proceeds of the sale of any other Deposited Property, in exchange for ADSs surrendered to the Depositary (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (iv) take such actions as may be required under applicable law in connection with its role as Depositary under the Deposit Agreement.

At any time after the Termination Date, the Depositary may sell the Deposited Property then held under the Deposit Agreement and shall after such sale hold un-invested the net proceeds of such sale, together with any other cash then held by it under the Deposit Agreement, in an un-segregated account and without liability for interest, for the pro rata benefit of the Holders whose ADSs have not theretofore been surrendered. After making such sale, the Depositary shall be discharged from all obligations under the Deposit Agreement except (i) to account for such net

proceeds and other cash (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (ii) as may be required at law in connection with the termination of the Deposit Agreement. After the Termination Date, the Company shall be discharged from all obligations under the Deposit Agreement, except for its obligations to the Depositary under Sections 5.8, 5.9 and 7.6 of the Deposit Agreement. The obligations under the terms of the Deposit Agreement of Holders and Beneficial Owners of ADSs outstanding as of the Termination Date shall survive the Termination Date and shall be discharged only when the applicable ADSs are presented by their Holders to the Depositary for cancellation under the terms of the Deposit Agreement (except as specifically provided in the Deposit Agreement).

Notwithstanding anything contained in the Deposit Agreement or any ADR, in connection with the termination of the Deposit Agreement, the Depositary may, independently and without the need for any action by the Company, make available to Holders of ADSs a means to withdraw the Deposited Securities represented by their ADSs and to direct the deposit of such Deposited Securities into an unsponsored American depositary shares program established by the Depositary, upon such terms and conditions as the Depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored American depositary shares program under the Securities Act, and to receipt by the Depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the Depositary.

ARTICLE VII

MISCELLANEOUS

Section 7.1 Counterparts. The Deposit Agreement may be executed in any number of counterparts, each of which shall be deemed an original and all of such counterparts together shall constitute one and the same agreement. Copies of the Deposit Agreement shall be maintained with the Depositary and shall be open to inspection by any Holder during business hours.

Section 7.2 No Third-Party Beneficiaries/Acknowledgments. The Deposit Agreement is for the exclusive benefit of the parties hereto (and their successors) and shall not be deemed to give any legal or equitable right, remedy or claim whatsoever to any other person, except to the extent specifically set forth in the Deposit Agreement. Nothing in the Deposit Agreement shall be deemed to give rise to a partnership or joint venture among the parties nor establish a fiduciary or similar relationship among the parties. The parties hereto acknowledge and agree that (i) Citibank and its Affiliates may at any time have multiple banking relationships with the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (ii) Citibank and its Affiliates may own and deal in any class of securities of the Company and its Affiliates and in ADSs, and may be engaged at any time in transactions in which parties adverse to the Company, the Holders, the Beneficial Owners or their respective Affiliates may have interests, (iii) the Depositary and its Affiliates may from time to time have in their possession non-public information about the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (iv) nothing contained in the Deposit Agreement shall (a) preclude Citibank or any of its

Affiliates from engaging in such transactions or establishing or maintaining such relationships, (b) obligate Citibank or any of its Affiliates to disclose such information, transactions or relationships, or to account for any profit made or payment received in such transactions or relationships, (v) the Depositary shall not be deemed to have knowledge of any information any other division of Citibank or any of its Affiliates may have about the Company, the Holders, the Beneficial Owners, or any of their respective Affiliates, and (vi) the Company, the Depositary, the Custodian and their respective agents and controlling persons may be subject to the laws and regulations of jurisdictions other than the United States, England, and the authority of courts and regulatory authorities of such other jurisdictions, and, consequently, the requirements and the limitations of such other laws and regulations, and the decisions and orders of such other courts and regulatory authorities, may affect the rights and obligations of the parties to the Deposit Agreement.

Section 7.3 Severability. In case any one or more of the provisions contained in the Deposit Agreement or in the ADRs should be or become invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein or therein shall in no way be affected, prejudiced or disturbed thereby.

The Depositary may execute transactions contemplated herein (e.g., foreign currency conversions, and sales of Deposited Property) through one or more divisions of Citibank or through one or more Citibank Affiliates, and any such entity may act as principal for its own account and not as agent, advisor, broker or fiduciary on behalf of any other person and may earn and retain revenue from such transactions, including, without, without limitation, transaction spreads, commissions, etc. The Depositary does not guarantee or represent that the price or rate obtained in any such transaction, or the method for obtaining such price or rate, will be the most favorable that could be obtained at that time.

Section 7.4 Holders and Beneficial Owners as Parties; Binding Effect. The Holders and Beneficial Owners from time to time of ADSs issued hereunder shall be parties to the Deposit Agreement and shall be bound by all of the terms and conditions hereof and of any ADR evidencing their ADSs by acceptance thereof or any beneficial interest therein.

Section 7.5 Notices. Any and all notices to be given to the Company shall be deemed to have been duly given if personally delivered or sent by mail, air courier or cable, telex or facsimile transmission, confirmed by letter personally delivered or sent by mail or air courier, addressed to Orchard Therapeutics plc, 108 Cannon Street, London EC4N 6EU, United Kingdom, Attention: John Ilett, General Counsel & Company Secretary, or to any other address which the Company may specify in writing to the Depositary.

Any and all notices to be given to the Depositary shall be deemed to have been duly given if personally delivered or sent by mail, air courier or cable, telex or facsimile transmission, confirmed by letter personally delivered or sent by mail or air courier, addressed to Citibank, N.A., 388 Greenwich Street, New York, New York 10013, U.S.A., Attention: Depositary Receipts Department, or to any other address which the Depositary may specify in writing to the Company.

Any and all notices to be given to any Holder shall be deemed to have been duly given **(a)** if personally delivered or sent by mail or cable, telex or facsimile transmission, confirmed by

letter, addressed to such Holder at the address of such Holder as it appears on the books of the Depositary or, if such Holder shall have filed with the Depositary a request that notices intended for such Holder be mailed to some other address, at the address specified in such request, or **(b)** if a Holder shall have designated such means of notification as an acceptable means of notification under the terms of the Deposit Agreement, by means of electronic messaging addressed for delivery to the e-mail address designated by the Holder for such purpose. Notice to Holders shall be deemed to be notice to Beneficial Owners for all purposes of the Deposit Agreement. Failure to notify a Holder or any defect in the notification to a Holder shall not affect the sufficiency of notification to other Holders or to the Beneficial Owners of ADSs held by such other Holders. Any notices given to DTC under the terms of the Deposit Agreement shall (unless otherwise specified by the Depositary) constitute notice to the DTC Participants who hold as the ADSs in their DTC accounts and to the Beneficial Owners of such ADSs.

Delivery of a notice sent by mail, air courier or cable, telex or facsimile transmission shall be deemed to be effective at the time when a duly addressed letter containing the same (or a confirmation thereof in the case of a cable, telex or facsimile transmission) is deposited, postage prepaid, in a post-office letter box or delivered to an air courier service, without regard for the actual receipt or time of actual receipt thereof by a Holder. The Depositary or the Company may, however, act upon any cable, telex or facsimile transmission received by it from any Holder, the Custodian, the Depositary, or the Company, notwithstanding that such cable, telex or facsimile transmission shall not be subsequently confirmed by letter.

Delivery of a notice by means of electronic messaging shall be deemed to be effective at the time of the initiation of the transmission by the sender (as shown on the sender's records), notwithstanding that the intended recipient retrieves the message at a later date, fails to retrieve such message, or fails to receive such notice on account of its failure to maintain the designated e-mail address, its failure to designate a substitute e-mail address or for any other reason.

Section 7.6 Governing Law and Jurisdiction. The Deposit Agreement and the ADRs shall be interpreted in accordance with, and all rights hereunder and thereunder and provisions hereof and thereof shall be governed by, the laws of the State of New York applicable to contracts made and to be wholly performed in that State. Notwithstanding anything contained in the Deposit Agreement, any ADR or any present or future provisions of the laws of the State of New York, the rights of holders of Shares and of any other Deposited Securities and the obligations and duties of the Company in respect of the holders of Shares and other Deposited Securities, as such, shall be governed by the laws of England and Wales (or, if applicable, such other laws as may govern the Deposited Securities).

Except as set forth in the following paragraph of this Section 7.6, the Company and the Depositary agree that the federal or state courts in the City of New York shall have jurisdiction to hear and determine any suit, action or proceeding and to settle any dispute between them that may arise out of or in connection with the Deposit Agreement and, for such purposes, each irrevocably submits to the non-exclusive jurisdiction of such courts. The Company hereby irrevocably designates, appoints and empowers Cogency Global Inc. (the "Agent") now at 10 East 40th Street 10th Floor, New York, New York 10016, as its authorized agent to receive and accept for and on its behalf, and on behalf of its properties, assets and revenues, service by mail of any and all legal

process, summons, notices and documents that may be served in any suit, action or proceeding brought against the Company in any federal or state court as described in the preceding sentence or in the next paragraph of this Section 7.6. If for any reason the Agent shall cease to be available to act as such, the Company agrees to designate a new agent in New York on the terms and for the purposes of this Section 7.6 reasonably satisfactory to the Depositary. The Company further hereby irrevocably consents and agrees to the service of any and all legal process, summons, notices and documents in any suit, action or proceeding against the Company, by service by mail of a copy thereof upon the Agent (whether or not the appointment of such Agent shall for any reason prove to be ineffective or such Agent shall fail to accept or acknowledge such service), with a copy mailed to the Company by registered or certified air mail, postage prepaid, to its address provided in Section 7.5. The Company agrees that the failure of the Agent to give any notice of such service to it shall not impair or affect in any way the validity of such service or any judgment rendered in any action or proceeding based thereon.

Notwithstanding the foregoing, the Depositary and the Company unconditionally agree that in the event that a Holder or Beneficial Owner brings a suit, action or proceeding against (a) the Company, (b) the Depositary in its capacity as Depositary under the Deposit Agreement or (c) against both the Company and the Depositary, in any such case, in any state or federal court of the United States, and the Depositary or the Company have any claim, for indemnification or otherwise, against each other arising out of the subject matter of such suit, action or proceeding, then the Company and the Depositary may pursue such claim against each other in the state or federal court in the United States in which such suit, action, or proceeding is pending and, for such purposes, the Company and the Depositary irrevocably submit to the non-exclusive jurisdiction of such courts. The Company agrees that service of process upon the Agent in the manner set forth in the preceding paragraph shall be effective service upon it for any suit, action or proceeding brought against it as described in this paragraph.

The Company irrevocably and unconditionally waives, to the fullest extent permitted by law, any objection that it may now or hereafter have to the laying of venue of any actions, suits or proceedings brought in any court as provided in this Section 7.6, and hereby further irrevocably and unconditionally waives and agrees not to plead or claim in any such court that any such action, suit or proceeding brought in any such court has been brought in an inconvenient forum.

The Company irrevocably and unconditionally waives, to the fullest extent permitted by law, and agrees not to plead or claim, any right of immunity from legal action, suit or proceeding, from setoff or counterclaim, from the jurisdiction of any court, from service of process, from attachment upon or prior to judgment, from attachment in aid of execution or judgment, from execution of judgment, or from any other legal process or proceeding for the giving of any relief or for the enforcement of any judgment, and consents to such relief and enforcement against it, its assets and its revenues in any jurisdiction, in each case with respect to any matter arising out of, or in connection with, the Deposit Agreement, any ADR or the Deposited Property.

EACH OF THE PARTIES TO THE DEPOSIT AGREEMENT (INCLUDING, WITHOUT LIMITATION, EACH HOLDER AND BENEFICIAL OWNER) IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL

PROCEEDING AGAINST THE COMPANY AND/OR THE DEPOSITARY ARISING OUT OF, OR RELATING TO, THE DEPOSIT AGREEMENT, ANY ADR AND ANY TRANSACTIONS CONTEMPLATED THEREIN (WHETHER BASED ON CONTRACT, TORT, COMMON LAW OR OTHERWISE).

The provisions of this Section 7.6 shall survive any termination of the Deposit Agreement, in whole or in part.

Section 7.7 Assignment. Subject to the provisions of Section 5.4, the Deposit Agreement may not be assigned by either the Company or the Depositary.

Section 7.8 Compliance with, and No Disclaimer under, U.S. Securities Laws.

(a) Notwithstanding anything in the Deposit Agreement to the contrary, the withdrawal or delivery of Deposited Securities will not be suspended by the Company or the Depositary except as would be permitted by Instruction I.A.(1) of the General Instructions to Form F-6 Registration Statement, as amended from time to time, under the Securities Act.

(b) Each of the parties to the Deposit Agreement (including, without limitation, each Holder and Beneficial Owner) acknowledges and agrees that no provision of the Deposit Agreement or any ADR shall, or shall be deemed to, disclaim any liability under the Securities Act or the Exchange Act, in each case to the extent established under applicable U.S. laws.

Section 7.9 English Law References. Any summary of English laws and regulations and of the terms of the Company's Articles of Association set forth in the Deposit Agreement have been provided by the Company solely for the convenience of Holders, Beneficial Owners and the Depositary. While such summaries are believed by the Company to be accurate as of the date of the Deposit Agreement, (i) they are summaries and as such may not include all aspects of the materials summarized applicable to a Holder or Beneficial Owner, and (ii) these laws and regulations and the Company's Articles of Association may change after the date of the Deposit Agreement. Neither the Depositary nor the Company has any obligation under the terms of the Deposit Agreement to update any such summaries.

Section 7.10 Titles and References.

(a) **Deposit Agreement.** All references in the Deposit Agreement to exhibits, articles, sections, subsections, and other subdivisions refer to the exhibits, articles, sections, subsections and other subdivisions of the Deposit Agreement unless expressly provided otherwise. The words "the Deposit Agreement", "herein", "hereof", "hereby", "hereunder", and words of similar import refer to the Deposit Agreement as a whole as in effect at the relevant time between the Company, the Depositary and the Holders and Beneficial Owners of ADSs and not to any particular subdivision unless expressly so limited. Pronouns in masculine, feminine and neuter gender shall be construed to include any other gender, and words in the singular form shall be construed to include the plural and *vice versa* unless the context otherwise requires. Titles to sections of the Deposit Agreement are included for convenience only and shall be disregarded in construing the language contained in the Deposit Agreement. References to "applicable laws and regulations" shall refer to laws and regulations applicable to ADRs, ADSs or Deposited Property as in effect at the relevant time of determination, unless otherwise required by law or regulation.

(b) **ADRs.** All references in any ADR(s) to paragraphs, exhibits, articles, sections, subsections, and other subdivisions refer to the paragraphs, exhibits, articles, sections, subsections and other subdivisions of the ADR(s) in question unless expressly provided otherwise. The words "the Receipt", "the ADR", "herein", "hereof", "hereby", "hereunder", and words of similar import used in any ADR refer to the ADR as a whole and as in effect at the relevant time, and not to any particular subdivision unless expressly so limited. Pronouns in masculine, feminine and neuter gender in any ADR shall be construed to include any other gender, and words in the singular form shall be construed to include the plural and *vice versa* unless the context otherwise requires. Titles to paragraphs of any ADR are included for convenience only and shall be disregarded in construing the language contained in the ADR. References to "applicable laws and regulations" shall refer to laws and regulations applicable to the Company, the Depositary, the Custodian, their agents and controlling persons, the ADRs, the ADSs and the Deposited Property as in effect at the relevant time of determination, unless otherwise required by law or regulation.

[*Signature Page Follows*]

IN WITNESS WHEREOF, ORCHARD THERAPEUTICS PLC and CITIBANK, N.A. have duly executed the Deposit Agreement as of the day and year first above set forth and all Holders and Beneficial Owners shall become parties hereto upon acceptance by them of ADSs issued in accordance with the terms hereof, or upon acquisition of any beneficial interest therein.

ORCHARD THERAPEUTICS PLC

By: _____
Name:
Title:

CITIBANK, N.A.

By: _____
Name:
Title:

EXHIBIT A

FORM OF ADR

Number _____ CUSIP NUMBER: _____

American Depositary Shares (each American Depositary Share representing the right to receive one (1) fully paid ordinary share)

AMERICAN DEPOSITARY RECEIPT

for

AMERICAN DEPOSITARY SHARES

representing

DEPOSITED ORDINARY SHARES

of

ORCHARD THERAPEUTICS PLC

(Incorporated under the laws of England and Wales)

CITIBANK, N.A., a national banking association organized and existing under the laws of the United States of America, as depositary (the "Depositary"), hereby certifies that is the owner of American Depositary Shares (hereinafter "ADS") representing deposited ordinary shares, including evidence of rights to receive such ordinary shares (the "Shares"), of Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales (the "Company"). As of the date of issuance of this ADR, each ADS represents the right to receive one (1) Share deposited under the Deposit Agreement (as hereinafter defined) with the Custodian, which at the date of issuance of this ADR is Citibank, N.A. (London) (the "Custodian"). The ADS(s)-to-Share(s) ratio is subject to amendment as provided in Articles IV and VI of the Deposit Agreement. The Depositary's Principal Office is located at 388 Greenwich Street, New York, New York 10013, U.S.A.

(1) **The Deposit Agreement.** This American Depositary Receipt is one of an issue of American Depositary Receipts ("ADRs"), all issued and to be issued upon the terms and conditions set forth in the Deposit Agreement, dated as of [●], 2018 (as amended and

supplemented from time to time, the "Deposit Agreement"), by and among the Company, the Depositary, and all Holders and Beneficial Owners from time to time of ADSs issued thereunder. The Deposit Agreement sets forth the rights and obligations of Holders and Beneficial Owners of ADSs and the rights and duties of the Depositary in respect of the Shares deposited thereunder and any and all other Deposited Property (as defined in the Deposit Agreement) from time to time received and held on deposit in respect of the ADSs. Copies of the Deposit Agreement are on file at the Principal Office of the Depositary and with the Custodian. Each Holder and each Beneficial Owner, upon acceptance of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement, shall be deemed for all purposes to (a) be a party to and bound by the terms of the Deposit Agreement and the applicable ADR(s), and (b) appoint the Depositary its attorney-in-fact, with full power to delegate, to act on its behalf and to take any and all actions contemplated in the Deposit Agreement and the applicable ADR(s), to adopt any and all procedures necessary to comply with applicable law and to take such action as the Depositary in its sole discretion may deem necessary or appropriate to carry out the purposes of the Deposit Agreement and the applicable ADR(s), the taking of such actions to be the conclusive determinant of the necessity and appropriateness thereof. The manner in which a Beneficial Owner holds ADSs (e.g., in a brokerage account vs. as registered holder) may affect the rights and obligations of, the manner in which, and the extent to which, services are made available to, Beneficial Owners pursuant to the terms of the Deposit Agreement.

The statements made on the face and reverse of this ADR are summaries of certain provisions of the Deposit Agreement and the Articles of Association of the Company (as in effect on the date of the signing of the Deposit Agreement) and are qualified by and subject to the detailed provisions of the Deposit Agreement and the Articles of Association, to which reference is hereby made.

All capitalized terms not defined herein shall have the meanings ascribed thereto in the Deposit Agreement.

The Depositary makes no representation or warranty as to the validity or worth of the Deposited Property. The Depositary has made arrangements for the acceptance of the ADSs into DTC. Each Beneficial Owner of ADSs held through DTC must rely on the procedures of DTC and the DTC Participants to exercise and be entitled to any rights attributable to such ADSs. The Depositary may issue Uncertificated ADSs subject, however, to the terms and conditions of Section 2.13 of the Deposit Agreement.

(2) **Surrender of ADSs and Withdrawal of Deposited Securities.** The Holder of this ADR (and of the ADSs evidenced hereby) shall be entitled to Delivery (at the Custodian's designated office) of the Deposited Securities at the time represented by the ADSs evidenced hereby upon satisfaction of each of the following conditions: (i) the Holder (or a duly-authorized attorney of the Holder) has duly Delivered ADSs to the Depositary at its Principal Office the ADSs evidenced hereby (and, if applicable, this ADR evidencing such ADSs) for the purpose of withdrawal of the Deposited Securities represented hereby, (ii) if applicable and so required by the Depositary, this ADR Delivered to the Depositary for such purpose has been properly endorsed in blank or is accompanied by proper instruments of transfer in blank (including signature guarantees in accordance with standard securities industry practice), (iii) if so required by the Depositary, the

Holder of the ADSs has executed and delivered to the Depositary a written order directing the Depositary to cause the Deposited Securities being withdrawn to be Delivered to or upon the written order of the person(s) designated in such order, and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case*, to the terms and conditions of this ADR evidencing the surrendered ADSs, of the Deposit Agreement, of the Company's Articles of Association and of any applicable laws and the rules of CREST, and to any provisions of or governing the Deposited Securities, in each case as in effect at the time thereof.

Upon satisfaction of each of the conditions specified above, the Depositary (i) shall cancel the ADSs Delivered to it (and, if applicable, this ADR(s) evidencing the ADSs so Delivered), (ii) shall direct the Registrar to record the cancellation of the ADSs so Delivered on the books maintained for such purpose, and (iii) shall direct the Custodian to Deliver, or cause the Delivery of, in each case, without unreasonable delay, the Deposited Securities represented by the ADSs so canceled together with any certificate or other document of title for the Deposited Securities, or evidence of the electronic transfer thereof (if available), as the case may be, to or upon the written order of the person(s) designated in the order delivered to the Depositary for such purpose, *subject however, in each case*, to the terms and conditions of the Deposit Agreement, of this ADR evidencing the ADS so canceled, of the Articles of Association of the Company, of any applicable laws and of the rules of CREST, and to the terms and conditions of or governing the Deposited Securities, in each case as in effect at the time thereof.

The Depositary shall not accept for surrender ADSs representing less than one (1) Share. In the case of Delivery to it of ADSs representing a number other than a whole number of Shares, the Depositary shall cause ownership of the appropriate whole number of Shares to be Delivered in accordance with the terms hereof, and shall, at the discretion of the Depositary, either (i) return to the person surrendering such ADSs the number of ADSs representing any remaining fractional Share, or (ii) sell or cause to be sold the fractional Share represented by the ADSs so surrendered and remit the proceeds of such sale (net of (a) applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld as a result of such sale) to the person surrendering the ADSs.

Notwithstanding anything else contained in this ADR or the Deposit Agreement, the Depositary may make delivery at the Principal Office of the Depositary of Deposited Property consisting of (i) any cash dividends or cash distributions, or (ii) any proceeds from the sale of any non-cash distributions, which are at the time held by the Depositary in respect of the Deposited Securities represented by the ADSs surrendered for cancellation and withdrawal. At the request, risk and expense of any Holder so surrendering ADSs represented by this ADR, and for the account of such Holder, the Depositary shall direct the Custodian to forward (to the extent permitted by law) any Deposited Property (other than Deposited Securities) held by the Custodian in respect of such ADSs to the Depositary for delivery at the Principal Office of the Depositary. Such direction shall be given by letter or, at the request, risk and expense of such Holder, by cable, telex or facsimile transmission.

(3) **Transfer, Combination and Split-up of ADRs.** The Registrar shall register the transfer of this ADR (and of the ADSs represented hereby) on the books maintained for such purpose and the Depositary shall (x) cancel this ADR and execute new ADRs evidencing the same aggregate number of ADSs as those evidenced by this ADR canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs, and (z) Deliver such new ADRs to or upon the order of the person entitled thereto, if each of the following conditions has been satisfied: (i) this ADR has been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a transfer thereof, (ii) this surrendered ADR has been properly endorsed or is accompanied by proper instruments of transfer (including signature guarantees in accordance with standard securities industry practice), (iii) this surrendered ADR has been duly stamped (if required by the laws of the State of New York or of the United States), and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case,* to the terms and conditions of this ADR, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

The Registrar shall register the split-up or combination of this ADR (and of the ADSs represented hereby) on the books maintained for such purpose and the Depositary shall (x) cancel this ADR and execute new ADRs for the number of ADSs requested, but in the aggregate not exceeding the number of ADSs evidenced by this ADR canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs, and (z) Deliver such new ADRs to or upon the order of the Holder thereof, if each of the following conditions has been satisfied: (i) this ADR has been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a split-up or combination hereof, and (ii) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case*, to the terms and conditions of this ADR, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

(4) **Pre-Conditions to Registration, Transfer, Etc.** As a condition precedent to the execution and Delivery, the registration of issuance, transfer, split-up, combination or surrender, of any ADS, the delivery of any distribution thereon, or the withdrawal of any Deposited Property, the Depositary or the Custodian may require (i) payment from the depositor of Shares or presenter of ADSs or of this ADR of a sum sufficient to reimburse it for any tax or other governmental charge and any stock transfer or registration fee with respect thereto (including any such tax or charge and fee with respect to Shares being deposited or withdrawn) and payment of any applicable fees and charges of the Depositary as provided in Section 5.9 and Exhibit B to the Deposit Agreement and in this ADR, (ii) the production of proof reasonably satisfactory to it as to the identity and genuineness of any signature or any other matter contemplated by Section 3.1 of the Deposit Agreement, and (iii) compliance with (A) any laws or governmental regulations relating to the execution and Delivery of this ADR or ADSs or to the withdrawal of Deposited Securities and (B) such reasonable regulations as the Depositary and the Company may establish consistent with the provisions of this ADR, if applicable, the Deposit Agreement and applicable law.

The issuance of ADSs against deposits of Shares generally or against deposits of particular Shares may be suspended, or the deposit of particular Shares may be refused, or the registration of transfer of ADSs in particular instances may be refused, or the registration of transfer of ADSs generally may be suspended, during any period when the transfer books of the Company, the Depositary, a Registrar or the Share Registrar are closed or if any such action is deemed necessary or advisable by the Depositary or the Company, in good faith, at any time or from time to time because of any requirement of law or regulation, any government or governmental body or commission or any securities exchange on which the ADSs or Shares are listed, or under any provision of the Deposit Agreement or this ADR, if applicable, or under any provision of, or governing, the Deposited Securities, or because of a meeting of shareholders of the Company or for any other reason, subject, in all cases to Section 7.8 of the Deposit Agreement and paragraph (25) of this ADR. Notwithstanding any provision of the Deposit Agreement or this ADR to the contrary, Holders are entitled to surrender outstanding ADSs to withdraw the Deposited Securities associated therewith at any time subject only to (i) temporary delays caused by closing the transfer books of the Depositary or the Company or the deposit of Shares in connection with voting at a shareholders' meeting or the payment of dividends, (ii) the payment of fees, taxes and similar charges, (iii) compliance with any U.S. or foreign laws or governmental regulations relating to the ADSs or to the withdrawal of the Deposited Securities, and (iv) other circumstances specifically contemplated by Instruction I.A.(l) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time).

(5) **Compliance With Information Requests.** Notwithstanding any other provision of the Deposit Agreement or this ADR, each Holder and Beneficial Owner of the ADSs represented hereby agrees to comply with requests from the Company pursuant to applicable law, the rules and requirements of any stock exchange on which the Shares or ADSs are, or will be, registered, traded or listed, or the Articles of Association of the Company, which are made to provide information, *inter alia*, as to the capacity in which such Holder or Beneficial Owner owns ADSs (and the Shares represented by such ADSs, as the case may be) and regarding the identity of any other person(s) interested in such ADSs (and the Shares represented by such ADSs, as the case may be) and the nature of such interest and various other matters, whether or not they are Holders and/or Beneficial Owners at the time of such request.

(6) **Ownership Restrictions.** Notwithstanding any other provision of this ADR or of the Deposit Agreement, the Company may restrict transfers of the Shares where such transfer might result in ownership of Shares exceeding limits imposed by applicable law or the Articles of Association of the Company. The Company may also restrict, in such manner as it deems appropriate, transfers of the ADSs where such transfer may result in the total number of Shares represented by the ADSs owned by a single Holder or Beneficial Owner to exceed any such limits. The Company may, in its sole discretion but subject to applicable law, instruct the Depositary to take action with respect to the ownership interest of any Holder or Beneficial Owner in excess of the limits set forth in the preceding sentence, including but not limited to, the imposition of restrictions on the transfer of ADSs, the removal or limitation of voting rights or the mandatory sale or disposition on behalf of a Holder or Beneficial Owner of the Shares represented by the ADSs held by such Holder or Beneficial Owner in excess of such limitations, if and to the extent such disposition is permitted by applicable law and the Articles of Association of the Company. Nothing herein or in the Deposit Agreement shall be interpreted as obligating the Depositary or the Company to ensure compliance with the ownership restrictions described herein or in Section 3.5 of the Deposit Agreement.

Notwithstanding any provision of this ADR or the Deposit Agreement and without limiting the foregoing, by being a Holder of this ADR (and of the ADSs evidenced hereby), the Holder agrees to provide such information as the Company may request in a disclosure notice (a "Disclosure Notice") given pursuant to the U.K. Companies Act 2006 (as amended from time to time and including any statutory modification or re-enactment thereof, the "Companies Act") or the Articles of Association of the Company. By accepting or holding this ADR, the Holder acknowledges that it understands that failure to comply with a Disclosure Notice may result in the imposition of sanctions against the Holder of the Shares in respect of which the non-complying person is or was, or appears to be or has been, interested as provided in the Companies Act and the Articles of Association which currently include, the withdrawal of the voting rights of such Shares and the imposition of restrictions on the rights to receive dividends on and to transfer such Shares.

(7) **Reporting Obligations and Regulatory Approvals.** Applicable laws and regulations may require holders and beneficial owners of Shares, including the Holders and Beneficial Owners of ADSs, to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. Holders and Beneficial Owners of ADSs are solely responsible for determining and complying with such reporting requirements and obtaining such approvals. Each Holder and each Beneficial Owner hereby agrees to make such determination, file such reports, and obtain such approvals to the extent and in the form required by applicable laws and regulations as in effect from time to time. Neither the Depositary, the Custodian, the Company or any of their respective agents or affiliates shall be required to take any actions whatsoever on behalf of Holders or Beneficial Owners to determine or satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

(8) **Liability for Taxes and Other Charges.** Any tax or other governmental charge payable by the Custodian or by the Depositary with respect to any Deposited Property, ADSs or this ADR shall be payable by the Holders and Beneficial Owners to the Depositary. The Company, the Custodian and/or the Depositary may withhold or deduct from any distributions made in respect of Deposited Property, and may sell for the account of a Holder and/or Beneficial Owner any or all of the Deposited Property and apply such distributions and sale proceeds in payment of, any taxes (including applicable interest and penalties) or charges that are or may be payable by Holders or Beneficial Owners in respect of the ADSs, Deposited Property and this ADR, the Holder and the Beneficial Owner hereof remaining liable for any deficiency. The Custodian may refuse the deposit of Shares and the Depositary may refuse to issue ADSs, to deliver ADRs, register the transfer of ADSs, register the split-up or combination of ADRs and (subject to paragraph (25) of this ADR and Section 7.8 of the Deposit Agreement) the withdrawal of Deposited Property until payment in full of such tax, charge, penalty or interest is received. Every Holder and Beneficial Owner agrees to indemnify the Depositary, the Company, the Custodian, and any of their agents, officers, employees and Affiliates for, and to hold each of them harmless from, any claims with respect to taxes (including applicable interest and penalties thereon) arising from any tax benefit obtained for such Holder and/or Beneficial Owner. The obligations of Holders and Beneficial Owners under this paragraph (8) and Section 3.2 of the Deposit Agreement shall survive any transfer of ADSs, any cancellation of ADSs and withdrawal of Deposited Securities, and the termination of the Deposit Agreement.

(9) **Representations and Warranties on Deposit of Shares.** Each person depositing Shares under the Deposit Agreement shall be deemed thereby to represent and warrant that (i) such Shares and the certificates therefor are duly authorized, validly allotted and issued, fully paid, not subject to any call for payment of further capital and legally obtained by such person, (ii) all preemptive (and similar) rights, if any, with respect to such Shares have been validly waived, disapplied or exercised, (iii) the person making such deposit is duly authorized so to do, (iv) the Shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, (v) the Shares presented for deposit are not, and the ADSs issuable upon such deposit will not be, Restricted Securities (except as contemplated in Section 2.14 of the Deposit Agreement), (vi) the Shares presented for deposit have not been stripped of any rights or entitlements, and (viii) the deposit of the Shares does not violate any applicable provisions of English law. Such representations and warranties shall survive the deposit and withdrawal of Shares, the issuance and cancellation of ADSs in respect thereof and the transfer of such ADSs. If any such representations or warranties are false in any way, the Company and the Depositary shall be authorized, at the cost and expense of the person depositing Shares, to take any and all actions necessary to correct the consequences thereof.

(10) **Proofs, Certificates and Other Information.** Any person presenting Shares for deposit, any Holder and any Beneficial Owner may be required, and every Holder and Beneficial Owner agrees, from time to time to provide to the Depositary and the Custodian such proof of citizenship or residence, taxpayer status, payment of all applicable taxes or other governmental charges, exchange control approval, legal or beneficial ownership of ADSs and Deposited Property, compliance with applicable laws, the terms of the Deposit Agreement or this ADR evidencing the ADSs and the provisions of, or governing, the Deposited Property, to execute such certifications and to make such representations and warranties, and to provide such other information and documentation (or, in the case of Shares in registered form presented for deposit, such information relating to the registration on the books of the Company or of the Share Registrar) as the Depositary or the Custodian may deem necessary or proper or as the Company may reasonably require by written request to the Depositary consistent with its obligations under the Deposit Agreement and this ADR. The Depositary and the Registrar, as applicable, may and at the reasonable request of the Company shall, to the extent practicable and subject to applicable law, withhold the execution or delivery or registration of transfer of any ADR or ADS or the distribution or sale of any dividend or distribution of rights or of the proceeds thereof or, to the extent not limited by paragraph (25) and Section 7.8 of the Deposit Agreement, the delivery of any Deposited Property until such proof or other information is filed or such certifications are executed, or such representations and warranties are made, or such other documentation or information are provided, in each case to the Depositary's, the Registrar's and the Company's satisfaction.

(11) **ADS Fees and Charges.** The following ADS fees are payable under the terms of the Deposit Agreement:

(i) ADS Issuance Fee: by any person for whom ADSs are issued (*e.g.*, an issuance upon a deposit of Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), excluding issuances as a result of distributions described in paragraph (iv) below, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) issued under the terms of the Deposit Agreement;

(ii) ADS Cancellation Fee: by any person for whom ADSs are being cancelled (*e.g.*, a cancellation of ADSs for Delivery of deposited shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) cancelled;

(iii) Cash Distribution Fee: by any Holder of ADSs to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of cash dividends or other cash distributions (*e.g.*, upon a sale of rights and other entitlements);

(iv) Stock Distribution /Rights Exercise Fee: by any Holder of ADS(s) to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of ADSs pursuant to (a) stock dividends or other free stock distributions, or (b) an exercise of rights to purchase additional ADSs;

(v) Other Distribution Fee: by any Holder of ADS(s) to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of securities other than ADSs or rights to purchase additional ADSs (*e.g.*, spin-off shares); and

(vi) Depositary Services Fee: by any Holder of ADS(s), a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held on the applicable record date(s) established by the Depositary.

The Company, Holders, Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with ADS issuances and cancellations, and persons for whom ADSs are issued or cancelled shall be responsible for the following ADS charges under the terms of the Deposit Agreement:

(a) taxes (including applicable interest and penalties) and other governmental charges;

(b) such registration fees as may from time to time be in effect for the registration of Shares or other Deposited Securities on the share register and applicable to transfers of Shares or other Deposited Securities to or from the name of the Custodian, the Depositary or any nominees upon the making of deposits and withdrawals, respectively;

(c) such cable, telex and facsimile transmission and delivery expenses as are expressly provided in the Deposit Agreement to be at the expense of the person depositing Shares or withdrawing Deposited Property or of the Holders and Beneficial Owners of ADSs;

(d) the expenses and charges incurred by the Depositary in the conversion of foreign currency (including transaction spreads);

(e) such fees and expenses as are incurred by the Depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to Deposited Property, ADSs and ADRs; and

(f) the fees and expenses incurred by the Depositary, the Custodian, or any nominee in connection with the delivery or servicing of Deposited Property.

All ADS fees and charges so payable may be deducted from distributions or must be remitted to the Depositary, or its designee, may, at any time and from time to time, be changed by agreement between the Depositary and Company but, in the case of ADS fees and charges payable by Holders and Beneficial Owners, only in the manner contemplated by paragraph (23) of this ADR and as contemplated in Section 6.1 of the Deposit Agreement. The Depositary shall provide, without charge, a copy of its latest ADS fee schedule to anyone upon request.

ADS fees and charges payable upon (i) the issuance of ADSs and (ii) the cancellation of ADSs will be payable by the person for whom the ADSs are so issued by the Depositary (in the case of ADS issuances) and by the person for whom ADSs are being cancelled by the Depositary (in the case of ADS cancellations). In the case of ADSs issued by the Depositary into DTC or presented to the Depositary via DTC, the ADS issuance and cancellation fees and charges will be payable by the DTC Participant(s) receiving the ADSs from the Depositary or the DTC Participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the Beneficial Owner(s) and will be charged by the DTC Participant(s) to the account(s) of the applicable Beneficial Owner(s) in accordance with the procedures and practices of the DTC Participant(s) as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are payable by Holders as of the applicable ADS Record Date established by the Depositary. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, the applicable Holders as of the ADS Record Date established by the Depositary will be invoiced for the amount of the ADS fees and charges and such ADS fees may be deducted from distributions made to Holders. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC and may be charged to the DTC Participants in accordance with the procedures and practices prescribed by DTC from time to time and the DTC Participants in turn charge the amount of such ADS fees and charges to the Beneficial Owners for whom they hold ADSs.

The Depositary may reimburse the Company for certain expenses incurred by the Company in respect of the ADR program established pursuant to the Deposit Agreement, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise,

upon such terms and conditions as the Company and the Depositary agree from time to time. The Company shall pay to the Depositary such fees and charges, and reimburse the Depositary for such out-of-pocket expenses, as the Depositary and the Company may agree from time to time. Responsibility for payment of such fees, charges and reimbursements may from time to time be changed by agreement between the Company and the Depositary. Unless otherwise agreed, the Depositary shall present its statement for such fees, charges and reimbursements to the Company once every three months. The charges and expenses of the Custodian are for the sole account of the Depositary.

The obligations of Holders and Beneficial Owners to pay ADS fees and charges shall survive the termination of the Deposit Agreement. As to any Depositary, upon the resignation or removal of such Depositary as described in Section 5.4 of the Deposit Agreement, the right to collect ADS fees and charges shall extend for those ADS fees and charges incurred prior to the effectiveness of such resignation or removal.

(12) **Title to ADRs.** Subject to the limitations contained in the Deposit Agreement and in this ADR, it is a condition of this ADR, and every successive Holder of this ADR by accepting or holding the same consents and agrees, that title to this ADR (and to each Certificated ADS evidenced hereby) shall be transferable upon the same terms as a certificated security under the laws of the State of New York, provided that, in the case of Certificated ADSs, this ADR has been properly endorsed or is accompanied by proper instruments of transfer. Notwithstanding any notice to the contrary, the Depositary and the Company may deem and treat the Holder of this ADR (that is, the person in whose name this ADR is registered on the books of the Depositary) as the absolute owner thereof for all purposes. Neither the Depositary nor the Company shall have any obligation nor be subject to any liability under the Deposit Agreement or this ADR to any holder of this ADR or any Beneficial Owner unless, in the case of a holder of ADSs, such holder is the Holder of this ADR registered on the books of the Depositary or, in the case of a Beneficial Owner, such Beneficial Owner, or the Beneficial Owner's representative, is the Holder registered on the books of the Depositary.

(13) **Validity of ADR.** The Holder(s) of this ADR (and the ADSs represented hereby) shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company unless this ADR has been (i) dated, (ii) signed by the manual or facsimile signature of a duly-authorized signatory of the Depositary, (iii) countersigned by the manual or facsimile signature of a duly-authorized signatory of the Registrar, and (iv) registered in the books maintained by the Registrar for the registration of issuances and transfers of ADRs. An ADR bearing the facsimile signature of a duly-authorized signatory of the Depositary or the Registrar, who at the time of signature was a duly authorized signatory of the Depositary or the Registrar, as the case may be, shall bind the Depositary, notwithstanding the fact that such signatory has ceased to be so authorized prior to the delivery of such ADR by the Depositary.

(14) **Available Information; Reports; Inspection of Transfer Books.** The Company is subject to the periodic reporting requirements of the Exchange Act and, accordingly, is required to file or furnish certain reports with the Commission. These reports can be retrieved from the Commission's website (www.sec.gov) and can be inspected and copied at the public reference

facilities maintained by the Commission located (as of the date of the Deposit Agreement) at 100 F Street, N.E., Washington D.C. 20549. The Depositary shall make available for inspection by Holders at its Principal Office, as promptly as practicable after receipt thereof, any reports and communications, including any proxy soliciting materials, received from the Company which are both (a) received by the Depositary, the Custodian, or the nominee of either of them as the holder of the Deposited Property and (b) made generally available to the holders of such Deposited Property by the Company.

The Registrar shall keep books for the registration of ADSs which at all reasonable times shall be open for inspection by the Company and by the Holders of such ADSs, provided that such inspection shall not be, to the Registrar's knowledge, for the purpose of communicating with Holders of such ADSs in the interest of a business or object other than the business of the Company or other than a matter related to the Deposit Agreement or the ADSs.

The Registrar may close the transfer books with respect to the ADSs, at any time or from time to time, when deemed necessary or advisable by it in good faith in connection with the performance of its duties hereunder, or at the reasonable written request of the Company subject, in all cases, to paragraph (25) and Section 7.8 of the Deposit Agreement.

Dated:

CITIBANK, N.A.
Transfer Agent and Registrar

By: _____
Authorized Signatory

CITIBANK, N.A.
as Depositary

By: _____
Authorized Signatory

The address of the Principal Office of the Depositary is 388 Greenwich Street, New York, New York 10013, U.S.A.

[FORM OF REVERSE OF ADR]

SUMMARY OF CERTAIN ADDITIONAL PROVISIONS

OF THE DEPOSIT AGREEMENT

(15) **Dividends and Distributions in Cash, Shares, etc.** (a) ***Cash Distributions***: Whenever the Company intends to make a distribution of a cash dividend or other cash distribution in respect of any Deposited Securities, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable for determining the holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt by the Depositary of a notice from the Company that it intends to make a distribution of a cash dividend or other cash distribution, the Depositary shall establish an ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement. Upon receipt of confirmation of receipt of (x) any cash dividend or other cash distribution on any Deposited Securities, or (y) proceeds from the sale of any Deposited Property held in respect of the ADSs under the terms of the Deposit Agreement, the Depositary will (i) if at the time of receipt thereof any amounts received in a Foreign Currency can, in the judgment of the Depositary (pursuant to Section 4.8 of the Deposit Agreement), be converted on a practicable basis into Dollars transferable to the United States, promptly convert or cause to be converted such cash dividend, distribution or proceeds into Dollars (on the terms described in Section 4.8 of the Deposit Agreement), (ii) if applicable and unless previously established, establish the ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement, and (iii) distribute promptly the amount thus received (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld in connection with the distribution) to the Holders entitled thereto as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date. The Depositary shall distribute only such amount, however, as can be distributed without attributing to any Holder a fraction of one cent, and any balance not so distributed shall be held by the Depositary (without liability for interest thereon) and shall be added to and become part of the next sum received by the Depositary for distribution to Holders of ADSs outstanding at the time of the next distribution. If the Company, the Custodian or the Depositary is required to withhold and does withhold from any cash dividend or other cash distribution in respect of any Deposited Securities, or from any cash proceeds from the sales of Deposited Property, an amount on account of taxes, duties or other governmental charges, the amount distributed to Holders on the ADSs shall be reduced accordingly. Such withheld amounts shall be forwarded by the Company, the Custodian or the Depositary to the relevant governmental authority. Evidence of payment thereof by the Company shall be forwarded by the Company to the Depositary upon request. The Depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable Holders and Beneficial Owners of ADSs until the distribution can be effected or the funds that the Depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions

contemplated in Section 4.1 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.1 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(b) ***Share Distributions*:** Whenever the Company intends to make a distribution that consists of a dividend in, or free distribution of, Shares, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution, specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt by the Depositary of a notice from the Company that it intends to make a distribution that consists of a dividend in, or free distribution of Shares, the Depositary shall establish the ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement. Upon receipt of confirmation from the Custodian of the receipt of the Shares so distributed by the Company, the Depositary shall either (i) subject to Section 5.9 of the Deposit Agreement, distribute to the Holders as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date, additional ADSs, which represent in the aggregate the number of Shares received as such dividend, or free distribution, subject to the other terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld), or (ii) if additional ADSs are not so distributed, take all actions necessary so that each ADS issued and outstanding after the ADS Record Date shall, to the extent permissible by law, thenceforth also represent rights and interests in the additional integral number of Shares distributed upon the Deposited Securities represented thereby (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes). In lieu of delivering fractional ADSs, the Depositary shall sell the number of Shares or ADSs, as the case may be, represented by the aggregate of such fractions and distribute the net proceeds upon the terms described in Section 4.1 of the Deposit Agreement.

In the event that the Depositary determines that any distribution in property (including Shares) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, or, if the Company in the fulfillment of its obligations under Section 5.7 of the Deposit Agreement, has furnished an opinion of U.S. counsel determining that Shares must be registered under the Securities Act or other laws in order to be distributed to Holders (and no such registration statement has been declared effective), the Depositary may dispose of all or a portion of such property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable, and the Depositary shall distribute the net proceeds of any such sale (after deduction of (a) applicable taxes required to be withheld and (b) fees and charges of, and the expenses incurred by, the Depositary) to Holders entitled thereto upon the terms of Section 4.1 of the Deposit Agreement. The Depositary shall hold and/or distribute any unsold balance of such property in accordance with the provisions of the Deposit Agreement. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.2 of the Deposit

Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.2 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(c) ***Elective Distributions in Cash or Shares***: Whenever the Company intends to make a distribution payable at the election of the holders of Deposited Securities in cash or in additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such elective distribution and whether or not it wishes such elective distribution to be made available to Holders of ADSs. Upon the timely receipt of a notice indicating that the Company wishes an elective distribution in cash or Shares to be made available to Holders of ADSs upon the terms described in the Deposit Agreement, the Company and the Depositary shall determine in accordance with the Deposit Agreement whether such distribution is lawful and reasonably practicable. The Depositary shall make such elective distribution available to Holders only if (i) the Company shall have timely requested that the elective distribution be made available to Holders, (ii) the Depositary shall have determined that such distribution is reasonably practicable and (iii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7 of the Deposit Agreement. If the above conditions are satisfied, the Depositary shall, subject to the terms and conditions of the Deposit Agreement, establish the ADS Record Date according to paragraph (16) and Section 4.9 of the Deposit Agreement and establish procedures to enable the Holder hereof to elect to receive the proposed distribution in cash or in additional ADSs. If a Holder elects to receive the distribution in cash, the distribution shall be made as in the case of a distribution in cash. If the Holder hereof elects to receive the distribution in additional ADSs, the distribution shall be made as in the case of a distribution in Shares upon the terms described in the Deposit Agreement. If such elective distribution is not reasonably practicable or if the Depositary did not receive satisfactory documentation set forth in the Deposit Agreement, the Depositary shall establish an ADS Record Date upon the terms of Section 4.9 of the Deposit Agreement and, to the extent permitted by law, distribute to Holders, on the basis of the same determination as is made in England and Wales in respect of the Shares for which no election is made, either (x) cash upon the terms described in Section 4.1 of the Deposit Agreement or (y) additional ADSs representing such additional Shares upon the terms described in Section 4.2 of the Deposit Agreement. Nothing herein or in the Deposit Agreement shall obligate the Depositary to make available to the Holder hereof a method to receive the elective distribution in Shares (rather than ADSs). There can be no assurance that the Holder hereof will be given the opportunity to receive elective distributions on the same terms and conditions as the holders of Shares. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.3 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.3 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(d) ***Distribution of Rights to Purchase Additional ADSs***: Whenever the Company intends to distribute to the holders of the Deposited Securities rights to subscribe for additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution and whether or not it wishes such rights to be made available to Holders of ADSs. Upon the timely receipt by the Depositary of a notice indicating that the Company wishes rights to subscribe for additional Shares to be made available to Holders of ADSs, the Depositary upon consultation with the Company, shall determine, whether it is lawful and reasonably practicable to make such rights available to the Holders. The Depositary shall make such rights available to any Holders only if (i) the Company shall have timely requested that such rights be made available to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7 of the Deposit Agreement, and (iii) the Depositary shall have determined that such distribution of rights is reasonably practicable. In the event any of the conditions set forth above are not satisfied or if the Company requests that the rights not be made available to Holders of ADSs, the Depositary shall proceed with the sale of the rights as described below. In the event all conditions set forth above are satisfied, the Depositary shall establish the ADS Record Date (upon the terms described in Section 4.9 of the Deposit Agreement) and establish procedures to (x) distribute rights to purchase additional ADSs (by means of warrants or otherwise), (y) enable the Holders to exercise such rights (upon payment of the subscription price and of the applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes), and (z) deliver ADSs upon the valid exercise of such rights. Nothing herein or in the Deposit Agreement shall obligate the Depositary to make available to the Holders a method to exercise rights to subscribe for Shares (rather than ADSs). If (i) the Company does not timely request the Depositary to make the rights available to Holders or requests that the rights not be made available to Holders, (ii) the Depositary fails to receive satisfactory documentation within the terms of Section 5,7 of the Deposit Agreement or determines it is not reasonably practicable to make the rights available to Holders, or (iii) any rights made available are not exercised and appear to be about to lapse, the Depositary shall determine whether it is lawful and reasonably practicable to sell such rights, in a riskless principal capacity, at such place and upon such terms (including public and private sale) as it may deem practicable. The Depositary shall, upon such sale, convert and distribute proceeds of such sale (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) upon the terms hereof and of Section 4.1 of the Deposit Agreement. If the Depositary is unable to make any rights available to Holders upon the terms described in Section 4.4(a) of the Deposit Agreement or to arrange for the sale of the rights upon the terms described in Section 4.4(b) of the Deposit Agreement, the Depositary shall allow such rights to lapse. The Depositary shall not be liable for (i) any failure to accurately determine whether it may be lawful or practicable to make such rights available to Holders in general or any Holders in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale or exercise, or (iii) the content of any materials forwarded to the Holders on behalf of the Company in connection with the rights distribution.

Notwithstanding anything herein or in Section 4.4 of the Deposit Agreement to the contrary, if registration (under the Securities Act or any other applicable law) of the rights or the securities to which any rights relate may be required in order for the Company to offer such rights or such securities to Holders and to sell the securities represented by such rights, the Depositary

will not distribute such rights to the Holders (i) unless and until a registration statement under the Securities Act (or other applicable law) covering such offering is in effect or (ii) unless the Company furnishes the Depositary opinion(s) of counsel for the Company in the United States and counsel to the Company in any other applicable country in which rights would be distributed, in each case satisfactory to the Depositary, to the effect that the offering and sale of such securities to Holders and Beneficial Owners are exempt from, or do not require registration under, the provisions of the Securities Act or any other applicable laws. In the event that the Company, the Depositary or the Custodian shall be required to withhold and does withhold from any distribution of Deposited Property (including rights) an amount on account of taxes or other governmental charges, the amount distributed to the Holders of ADSs shall be reduced accordingly. In the event that the Depositary determines that any distribution of Deposited Property (including Shares and rights to subscribe therefor) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, the Depositary may dispose of all or a portion of such Deposited Property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable to pay any such taxes or charges.

There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive or exercise rights on the same terms and conditions as the holders of Shares or be able to exercise such rights. Nothing herein or in the Deposit Agreement shall obligate the Company to file any registration statement in respect of any rights or Shares or other securities to be acquired upon the exercise of such rights.

(e) ***Distributions other than Cash, Shares or Rights to Purchase Shares***: Whenever the Company intends to distribute to the holders of Deposited Securities property other than cash, Shares or rights to purchase additional Shares, the Company shall give timely notice thereof to the Depositary and shall indicate whether or not it wishes such distribution to be made to Holders of ADSs. Upon receipt of a notice indicating that the Company wishes property other than cash, Shares or rights to purchase additional Shares to be made to Holders of ADSs, the Depositary shall consult with the Company, and the Company shall assist the Depositary, to determine whether such distribution to Holders is lawful and reasonably practicable. The Depositary shall not make such distribution unless (i) the Company shall have requested the Depositary to make such distribution to Holders, (ii) the Depositary shall have received the documentation contemplated in the Deposit Agreement, and (iii) the Depositary shall have determined that such distribution is reasonably practicable. Upon satisfaction of such conditions, the Depositary shall distribute the property so received to the Holders of record, as of the ADS Record Date, in proportion to the number of ADSs held by them respectively and in such manner as the Depositary may deem practicable for accomplishing such distribution (i) upon receipt of payment or net of the applicable fees and charges of, and expenses incurred by, the Depositary, and (ii) net of any applicable taxes required to be withheld. The Depositary may dispose of all or a portion of the property so distributed and deposited, in such amounts and in such manner (including public or private sale) as the Depositary may deem practicable or necessary to satisfy any taxes (including applicable interest and penalties) or other governmental charges applicable to the distribution.

If the conditions above are not satisfied, the Depositary shall sell or cause such property to be sold in a public or private sale, at such place or places and upon such terms as it may deem

practicable and shall (i) cause the proceeds of such sale, if any, to be converted into Dollars and (ii) distribute the proceeds of such conversion received by the Depositary (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) to the Holders as of the ADS Record Date upon the terms hereof and of the Deposit Agreement. If the Depositary is unable to sell such property, the Depositary may dispose of such property for the account of the Holders in any way it deems reasonably practicable under the circumstances.

Neither the Depositary nor the Company shall be liable for (i) any failure to accurately determine whether it is lawful or practicable to make the property described in Section 4.5 of the Deposit Agreement available to Holders in general or any Holders in particular, nor (ii) any loss incurred in connection with the sale or disposal of such property.

(f) ***Distributions with Respect to Deposited Securities in Bearer Form***: Subject to the terms of this paragraph (15) and Article IV of the Deposit Agreement, distributions in respect of Deposited Securities that are held by the Depositary or the Custodian in bearer form shall be made to the Depositary for the account of the respective Holders of ADS(s) with respect to which any such distribution is made upon due presentation by the Depositary or the Custodian to the Company of any relevant coupons, talons, or certificates. The Company shall promptly notify the Depositary of such distributions. The Depositary or the Custodian shall promptly present such coupons, talons or certificates, as the case may be, in connection with any such distribution.

(16) **Redemption.** If the Company intends to exercise any right of redemption in respect of any of the Deposited Securities, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the intended date of redemption which notice shall set forth the particulars of the proposed redemption. Upon timely receipt of notice from the Company that it intends to exercise its right of redemption in respect of any of the Deposited Securities, and satisfactory documentation, and, after consultation between the Depositary and the Custodian, upon determining that such proposed redemption is practicable, the Depositary shall provide to each Holder a notice setting forth the Company's intention to exercise the redemption rights and any other particulars set forth in the Company's notice to the Depositary. The Depositary shall instruct the Custodian to present to the Company the Deposited Securities in respect of which redemption rights are being exercised against payment of the applicable redemption price. Upon receipt of confirmation from the Custodian that the redemption has taken place and that funds representing the redemption price have been received, the Depositary shall convert, transfer, and distribute the proceeds (net of applicable (a) fees and charges of, and the expenses incurred by, the Depositary, and (b) taxes), retire ADSs and cancel ADRs, if applicable, upon delivery of such ADSs by Holders thereof and the terms set forth in Sections 4.1 and 6.2 of the Deposit Agreement. If less than all outstanding Deposited Securities are redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as may be determined by the Depositary after consultation with the Company. The redemption price per ADS shall be the dollar equivalent of the per share amount received by the Depositary (adjusted to reflect the ADS(s)-to-Share(s) ratio) upon the redemption of the Deposited Securities represented by ADSs (subject to the terms of Section 4.8 of the Deposit Agreement and the applicable fees and charges of, and expenses incurred by, the Depositary, and applicable taxes) multiplied by the number of Deposited Securities represented by each ADS redeemed. Notwithstanding anything contained in the Deposit Agreement to the

contrary, in the event the Company fails to give the Depositary timely notice of the proposed redemption provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.7 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.7 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(17) **Fixing of ADS Record Date.** Whenever (a) the Depositary shall receive notice of the fixing of a record date by the Company for the determination of holders of Deposited Securities entitled to receive any distribution (whether in cash, Shares, rights or other distribution), (b) for any reason the Depositary causes a change in the number of Shares that are represented by each ADS, (c) the Depositary shall receive notice of any meeting of, or solicitation of consents or proxies of, holders of Shares or other Deposited Securities, or (d) the Depositary shall find it necessary or convenient in connection with the giving of any notice, solicitation of any consent or any other matter, the Depositary shall fix a record date (the "ADS Record Date") for the determination of the Holders of ADS(s) who shall be entitled to receive such distribution, to give instructions for the exercise of voting rights at any such meeting, to give or withhold such consent, to receive such notice or solicitation or to otherwise take action, or to exercise the rights of Holders with respect to such changed number of Shares represented by each ADS. The Depositary shall make reasonable efforts to establish the ADS Record Date as closely as practicable to the applicable record date for the Deposited Securities (if any) set by the Company in England and Wales and shall not announce the establishment of any ADS Record Date prior to the relevant corporate actions having been made public by the Company (if such corporate action affects the Deposited Securities). Subject to applicable law, the terms and conditions of this ADR, Sections 4.1 through 4.8 of the Deposit Agreement and the other terms and conditions of the Deposit Agreement, only the Holders of ADSs at the close of business in New York on such ADS Record Date shall be entitled to receive such distribution, to give such voting instructions, to receive such notice or solicitation, or otherwise take action.

(18) **Voting of Deposited Securities.** As soon as practicable after receipt of notice of any meeting at which the holders of Deposited Securities are entitled to vote, or of solicitation of consents or proxies from holders of Deposited Securities, the Depositary shall fix the ADS Record Date in respect of such meeting or solicitation of consent or proxy in accordance with Section 4.9 of the Deposit Agreement. The Depositary shall, if requested by the Company in writing in a timely manner (the Depositary having no obligation to take any further action if the request shall not have been received by the Depositary at least thirty (30) days prior to the date of such vote or meeting), at the Company's expense and provided no U.S. legal prohibitions exist, distribute as soon as practicable after receipt thereof to Holders as of the ADS Record Date: (a) such notice of meeting or solicitation of consent or proxy, (b) a statement that the Holders at the close of business on the ADS Record Date will be entitled, subject to any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of or governing the Deposited Securities (which provisions, if any, shall be summarized in pertinent part by the Company), to instruct the Depositary as to the exercise of the voting rights, if any, pertaining to the Deposited Securities represented by such Holder's ADSs, and (c) a brief statement as to the manner and timing (such timing to be determined after consultation with the

Company) in which such voting instructions may be given to the Depositary or in which voting instructions may be deemed to have been given in accordance with Section 4.10 of the Deposit Agreement if no instructions are received prior to the deadline set for such purposes to the Depositary to give a discretionary proxy to a person designated by the Company. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to timely request that the Depositary distribute the information as provided for in Section 4.10 of the Deposit Agreement, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.10 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.10 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Notwithstanding anything contained in the Deposit Agreement or this ADR, with the Company's prior written consent, the Depositary may, to the extent not prohibited by law or regulations, or by the requirements of any stock exchange on which the ADSs may be listed, in lieu of distribution of the materials provided to the Depositary in connection with any meeting of, or solicitation of consents or proxies from, holders of Deposited Securities, distribute to the Holders a notice that provides Holders with, or otherwise publicize to Holders, instructions on how to retrieve such materials or receive such materials upon request (*e.g.*, by reference to a website containing the materials for retrieval or a contact for requesting copies of the materials).

The Depositary has been advised by the Company that the Articles of Association (as in effect on the date of the Deposit Agreement), provide that voting at any meeting of shareholders is by show of hands unless a poll is demanded. The Depositary will not join in demanding a poll, whether or not requested to do so by Holders of ADSs. Under the Articles of Association (as in effect on the date of the Deposit Agreement), a poll may be demanded by (i) the chairman of the general meeting; (ii) by at least two members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting; (iii) by any member of members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting and/or one tenth of the aggregate sum of the total sum paid up on all shares of the Company; or (iv) by any member or members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

Voting instructions may be given only in respect of a number of ADSs representing an integral number of Deposited Securities. Upon the timely receipt from a Holder of ADSs as of the ADS Record Date of voting instructions in the manner specified by the Depositary, the Depositary shall endeavor, insofar as practicable and permitted under any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of the Deposited Securities, to vote, or cause the Custodian to vote, the Deposited Securities (in person or

by proxy) represented by such Holder's ADSs as follows: (i) in the event voting takes place at a shareholders' meeting by show of hands, the Depositary will instruct the Custodian to vote all Deposited Securities in accordance with the voting instructions received from a majority of Holders of ADSs who provided voting instructions and (ii) in the event voting takes place at a shareholders' meeting by poll, the Depositary will instruct the Custodian to vote the Deposited Securities in accordance with the voting instructions received from the Holders of ADSs. If the Depositary does not receive voting instructions from a Holder as of the ADS Record Date on or before the date established by the Depositary for such purpose, such Holder shall be deemed, and the Depositary shall deem such Holder, to have instructed the Depositary to give a discretionary proxy to a person designated by the Company to vote the Deposited Securities; provided, however, that no such discretionary proxy shall be given by the Depositary with respect to any matter to be voted upon as to which the Company informs the Depositary that (a) the Company does not wish such proxy to be given, (b) substantial opposition exists, or (c) the rights of holders of Deposited Securities may be adversely affected.

Deposited Securities represented by ADSs for which no timely voting instructions are received by the Depositary from the Holder shall not be voted (except as contemplated herein and in Section 4.10 of the Deposit Agreement). Neither the Depositary nor the Custodian shall under any circumstances exercise any discretion as to voting and neither the Depositary nor the Custodian shall vote, attempt to exercise the right to vote, or in any way make use of, for purposes of establishing a quorum or otherwise, the Deposited Securities represented by ADSs, except pursuant to and in accordance with the voting instructions timely received from Holders or as otherwise contemplated herein or in the Deposit Agreement. If the Depositary timely receives voting instructions from a Holder which fail to specify the manner in which the Depositary is to vote the Deposited Securities represented by such Holder's ADSs, the Depositary will deem such Holder (unless otherwise specified in the notice distributed to Holders) to have instructed the Depositary to vote in favor of the items set forth in such voting instructions.

Notwithstanding anything else contained in this ADR or the Deposit Agreement, the Depositary shall, if so requested in writing by the Company, represent all Deposited Securities (whether or not voting instructions have been received in respect of such Deposited Securities from Holders as of the ADS Record Date) for the sole purpose of establishing quorum at a meeting of shareholders.

Notwithstanding anything else contained in the Deposit Agreement or this ADR, the Depositary shall not have any obligation to take any action with respect to any meeting, or solicitation of consents or proxies, of holders of Deposited Securities if the taking of such action would violate U.S. or English laws. The Company agrees to take any and all actions reasonably necessary and as permitted by the laws of England and Wales to enable Holders and Beneficial Owners to exercise the voting rights accruing to the Deposited Securities and to deliver to the Depositary an opinion of U.S. counsel addressing any actions requested to be taken if so reasonably requested by the Depositary.

There can be no assurance that Holders generally or any Holder in particular will receive the notice described above with sufficient time to enable the Holder to return voting instructions to the Depositary in a timely manner.

(19) **Changes Affecting Deposited Securities.** Upon any change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of Deposited Securities, or upon any recapitalization, reorganization, merger, consolidation or sale of assets affecting the Company or to which it is a party, any property which shall be received by the Depositary or the Custodian in exchange for, or in conversion of, or replacement of, or otherwise in respect of, such Deposited Securities shall, to the extent permitted by law, be treated as new Deposited Property under the Deposit Agreement, and this ADR shall, subject to the provisions of the Deposit Agreement, this ADR evidencing such ADSs and applicable law, represent the right to receive such additional or replacement Deposited Property. In giving effect to such change, split-up, cancellation, consolidation or other reclassification of Deposited Securities, recapitalization, reorganization, merger, consolidation or sale of assets, the Depositary may, with the Company's approval, and shall, if the Company shall so request, subject to the terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes) and receipt of an opinion of counsel to the Company satisfactory to the Depositary that such actions are not in violation of any applicable laws or regulations, (i) issue and deliver additional ADSs as in the case of a stock dividend on the Shares, (ii) amend the Deposit Agreement and the applicable ADRs, (iii) amend the applicable Registration Statement(s) on Form F-6 as filed with the Commission in respect of the ADSs, (iv) call for the surrender of outstanding ADRs to be exchanged for new ADRs, and (v) take such other actions as are appropriate to reflect the transaction with respect to the ADSs. Notwithstanding the foregoing, in the event that any Deposited Property so received may not be lawfully distributed to some or all Holders, the Depositary may, with the Company's approval, and shall, if the Company requests, subject to receipt of an opinion of Company's counsel satisfactory to the Depositary that such action is not in violation of any applicable laws or regulations, sell such Deposited Property at public or private sale, at such place or places and upon such terms as it may deem proper and may allocate the net proceeds of such sales (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) for the account of the Holders otherwise entitled to such Deposited Property upon an averaged or other practicable basis without regard to any distinctions among such Holders and distribute the net proceeds so allocated to the extent practicable as in the case of a distribution received in cash pursuant to Section 4.1 of the Deposit Agreement. The Depositary shall not be responsible for (i) any failure to determine that it may be lawful or practicable to make such Deposited Property available to Holders in general or to any Holder in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or (iii) any liability to the purchaser of such Deposited Property.

(20) **Exoneration.** Notwithstanding anything contained in the Deposit Agreement or any ADR, neither the Depositary nor the Company shall be obligated to do or perform any act which is inconsistent with the provisions of the Deposit Agreement or incur any liability (to the extent not limited by paragraph (25) hereof) (i) if the Depositary, the Custodian, the Company or their respective agents shall be prevented or forbidden from, or delayed in, doing or performing any act or thing required or contemplated by the terms of the Deposit Agreement and this ADR, by reason of any provision of any present or future law or regulation of the United States, England and Wales or any other country, or of any other governmental authority or regulatory authority or stock exchange, or on account of potential criminal or civil penalties or restraint, or by reason of any provision, present or future, of the Articles of Association of the Company or any provision of or governing any Deposited Securities, or by reason of any act of God or war or other circumstances

beyond its control (including, without limitation, nationalization, expropriation, currency restrictions, work stoppage, strikes, civil unrest, acts of terrorism, revolutions, rebellions, explosions and computer failure), (ii) by reason of any exercise of, or failure to exercise, any discretion provided for in the Deposit Agreement or in the Articles of Association of the Company or provisions of or governing Deposited Securities, (iii) for any action or inaction in reliance upon the advice of or information from legal counsel, accountants, any person presenting Shares for deposit, any Holder, any Beneficial Owner or authorized representative thereof, or any other person believed by it in good faith to be competent to give such advice or information, (iv) for the inability by a Holder or Beneficial Owner to benefit from any distribution, offering, right or other benefit which is made available to holders of Deposited Securities but is not, under the terms of the Deposit Agreement, made available to Holders of ADSs, (v) for any action or inaction of any clearing or settlement system (and any participant thereof) for the Deposited Property or the ADSs, or (vi) for any consequential or punitive damages (including lost profits) for any breach of the terms of the Deposit Agreement. The Depositary, its controlling persons, its agents, any Custodian and the Company, its controlling persons and its agents may rely and shall be protected in acting upon any written notice, request or other document believed by it to be genuine and to have been signed or presented by the proper party or parties.

(21) **Standard of Care.** The Company and the Depositary assume no obligation and shall not be subject to any liability under the Deposit Agreement or this ADR to any Holder(s) or Beneficial Owner(s), except that the Company and the Depositary agree to perform their respective obligations specifically set forth in the Deposit Agreement or this ADR without negligence or bad faith. Without limitation of the foregoing, neither the Depositary, nor the Company, nor any of their respective controlling persons, or agents, shall be under any obligation to appear in, prosecute or defend any action, suit or other proceeding in respect of any Deposited Property or in respect of the ADSs, which in its opinion may involve it in expense or liability, unless indemnity satisfactory to it against all expense (including fees and disbursements of counsel) and liability be furnished as often as may be required (and no Custodian shall be under any obligation whatsoever with respect to such proceedings, the responsibility of the Custodian being solely to the Depositary).

The Depositary and its agents shall not be liable for any failure to carry out any instructions to vote any of the Deposited Securities, or for the manner in which any vote is cast or the effect of any vote, provided that any such action or omission is in good faith and without negligence and in accordance with the terms of the Deposit Agreement. The Depositary shall not incur any liability for any failure to accurately determine that any distribution or action may be lawful or reasonably practicable, for the content of any information submitted to it by the Company for distribution to the Holders or for any inaccuracy of any translation thereof, for any investment risk associated with acquiring an interest in the Deposited Property, for the validity or worth of the Deposited Property, for the value of any Deposited Property or any distribution thereon, for any interest on Deposited Property, for any tax consequences that may result from the ownership of ADSs, Shares or other Deposited Property, for the credit-worthiness of any third party, for allowing any rights to lapse upon the terms of the Deposit Agreement, for the failure or timeliness of any notice from the Company, or for any action of or failure to act by, or any information provided or not provided by, DTC or any DTC Participant.

The Depositary shall not be liable for any acts or omissions made by a successor depositary whether in connection with a previous act or omission of the Depositary or in connection with any matter arising wholly after the removal or resignation of the Depositary, provided that in connection with the issue out of which such potential liability arises the Depositary performed its obligations without negligence or bad faith while it acted as Depositary for the Company.

(22) **Resignation and Removal of the Depositary; Appointment of Successor Depositary.** The Depositary may at any time resign as Depositary under the Deposit Agreement by written notice of resignation delivered to the Company, such resignation to be effective on the earlier of (i) the 90th day after delivery thereof to the Company (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2 of the Deposit Agreement), or (ii) the appointment by the Company of a successor depositary and its acceptance of such appointment as provided in the Deposit Agreement. The Depositary may at any time be removed by the Company by written notice of such removal, which removal shall be effective on the later of (i) the 90th day after delivery thereof to the Depositary (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2 of the Deposit Agreement), or (ii) upon the appointment by the Company of a successor depositary and its acceptance of such appointment as provided in the Deposit Agreement. In case at any time the Depositary acting hereunder or under the Deposit Agreement shall resign or be removed, the Company shall use its best efforts to appoint a successor depositary, which shall be a bank or trust company having an office in the Borough of Manhattan, the City of New York. Every successor depositary shall be required by the Company to execute and deliver to its predecessor and to the Company an instrument in writing accepting its appointment hereunder, and thereupon such successor depositary, without any further act or deed (except as required by applicable law), shall become fully vested with all the rights, powers, duties and obligations of its predecessor (other than as contemplated in Sections 5.8 and 5.9 of the Deposit Agreement). The predecessor depositary, upon payment of all sums due it and on the written request of the Company shall (i) execute and deliver an instrument transferring to such successor all rights and powers of such predecessor hereunder (other than as contemplated in Sections 5.8 and 5.9 of the Deposit Agreement), (ii) duly assign, transfer and deliver all of the Depositary's right, title and interest to the Deposited Property to such successor, and (iii) deliver to such successor a list of the Holders of all outstanding ADSs and such other information relating to ADSs and Holders thereof as the successor may reasonably request. Any such successor depositary shall promptly provide notice of its appointment to such Holders. Any entity into or with which the Depositary may be merged or consolidated shall be the successor of the Depositary without the execution or filing of any document or any further act.

(23) **Amendment/Supplement.** Subject to the terms and conditions of this paragraph 23, and Section 6.1 of the Deposit Agreement and applicable law, this ADR and any provisions of the Deposit Agreement may at any time and from time to time be amended or supplemented by written agreement between the Company and the Depositary in any respect which they may deem necessary or desirable without the prior written consent of the Holders or Beneficial Owners. Any amendment or supplement which shall impose or increase any fees or charges (other than charges in connection with foreign exchange control regulations, and taxes and other governmental charges, delivery and other such expenses), or which shall otherwise materially prejudice any substantial existing right of Holders or Beneficial Owners, shall not, however, become effective as

to outstanding ADSs until the expiration of thirty (30) days after notice of such amendment or supplement shall have been given to the Holders of outstanding ADSs. Notice of any amendment to the Deposit Agreement or any ADR shall not need to describe in detail the specific amendments effectuated thereby, and failure to describe the specific amendments in any such notice shall not render such notice invalid, provided, however, that, in each such case, the notice given to the Holders identifies a means for Holders and Beneficial Owners to retrieve or receive the text of such amendment (*e.g.*, upon retrieval from the Commission's, the Depositary's or the Company's website or upon request from the Depositary). The parties hereto agree that any amendments or supplements which (i) are reasonably necessary (as agreed by the Company and the Depositary) in order for (a) the ADSs to be registered on Form F-6 under the Securities Act or (b) the ADSs to be settled solely in electronic book-entry form and (ii) do not in either such case impose or increase any fees or charges to be borne by Holders, shall be deemed not to materially prejudice any substantial rights of Holders or Beneficial Owners. Every Holder and Beneficial Owner at the time any amendment or supplement so becomes effective shall be deemed, by continuing to hold such ADSs, to consent and agree to such amendment or supplement and to be bound by the Deposit Agreement and this ADR, if applicable, as amended or supplemented thereby. In no event shall any amendment or supplement impair the right of the Holder to surrender such ADS and receive therefor the Deposited Securities represented thereby, except in order to comply with mandatory provisions of applicable law. Notwithstanding the foregoing, if any governmental body should adopt new laws, rules or regulations which would require an amendment of, or supplement to, the Deposit Agreement to ensure compliance therewith, the Company and the Depositary may amend or supplement the Deposit Agreement and this ADR at any time in accordance with such changed laws, rules or regulations. Such amendment or supplement to the Deposit Agreement and this ADR in such circumstances may become effective before a notice of such amendment or supplement is given to Holders or within any other period of time as required for compliance with such laws, rules or regulations.

(24) **Termination.** The Depositary shall, at any time at the written direction of the Company, terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. If ninety (90) days shall have expired after (i) the Depositary shall have delivered to the Company a written notice of its election to resign, or (ii) the Company shall have delivered to the Depositary a written notice of the removal of the Depositary, and, in either case, a successor depositary shall not have been appointed and accepted its appointment as provided in Section 5.4 of the Deposit Agreement, the Depositary may terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. The date so fixed for termination of the Deposit Agreement in any termination notice so distributed by the Depositary to the Holders of ADSs is referred to as the "Termination Date". Until the Termination Date, the Depositary shall continue to perform all of its obligations under the Deposit Agreement, and the Holders and Beneficial Owners will be entitled to all of their rights under the Deposit Agreement. If any ADSs shall remain outstanding after the Termination Date, the Registrar and the Depositary shall not, after the Termination Date, have any obligation to perform any further acts under the Deposit Agreement, except that the Depositary shall, subject, in each case, to the terms and conditions of the Deposit Agreement, continue to (i) collect dividends and other distributions pertaining to Deposited Securities, (ii) sell Deposited Property received in respect of Deposited

Securities, (iii) deliver Deposited Securities, together with any dividends or other distributions received with respect thereto and the net proceeds of the sale of any other Deposited Property, in exchange for ADSs surrendered to the Depositary (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (iv) take such actions as may be required under applicable law in connection with its role as Depositary under the Deposit Agreement. At any time after the Termination Date, the Depositary may sell the Deposited Property then held under the Deposit Agreement and shall after such sale hold un-invested the net proceeds of such sale, together with any other cash then held by it under the Deposit Agreement, in an un-segregated account and without liability for interest, for the pro rata benefit of the Holders whose ADSs have not theretofore been surrendered. After making such sale, the Depositary shall be discharged from all obligations under the Deposit Agreement except (i) to account for such net proceeds and other cash (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (ii) as may be required at law in connection with the termination of the Deposit Agreement. After the Termination Date, the Company shall be discharged from all obligations under the Deposit Agreement, except for its obligations to the Depositary under Sections 5.8, 5.9 and 7.6 of the Deposit Agreement. The obligations under the terms of the Deposit Agreement of Holders and Beneficial Owners of ADSs outstanding as of the Termination Date shall survive the Termination Date and shall be discharged only when the applicable ADSs are presented by their Holders to the Depositary for cancellation under the terms of the Deposit Agreement (except as specifically provided in the Deposit Agreement).

Notwithstanding anything contained in the Deposit Agreement or this ADR, in connection with the termination of the Deposit Agreement, the Depositary may, independently and without the need for any action by the Company, make available to Holders of ADSs a means to withdraw the Deposited Securities represented by their ADSs and to direct the deposit of such Deposited Securities into an unsponsored American depositary shares program established by the Depositary, upon such terms and conditions as the Depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored American depositary shares program under the Securities Act, and to receipt by the Depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the Depositary.

(25) **Compliance with and No Disclaimer under, U.S. Securities Laws.**

(a) Notwithstanding any provisions in this ADR or the Deposit Agreement to the contrary, the withdrawal or delivery of Deposited Securities will not be suspended by the Company or the Depositary except as would be permitted by Instruction I.A.(1) of the General Instructions to the Form F-6 Registration Statement, as amended from time to time, under the Securities Act.

(b) Each of the parties to the Deposit Agreement (including, without limitation, each Holder and Beneficial Owner) acknowledges and agrees that no provision of the Deposit Agreement or any ADR shall, or shall be deemed to, disclaim any liability under the Securities Act or the Exchange Act, in each case to the extent established under applicable U.S. laws.

(26) **No Third Party Beneficiaries/Acknowledgements**. The Deposit Agreement is for the exclusive benefit of the parties hereto (and their successors) and shall not be deemed to give any legal or equitable right, remedy or claim whatsoever to any other person, except to the extent specifically set forth in the Deposit Agreement. Nothing in the Deposit Agreement shall be deemed to give rise to a partnership or joint venture among the parties nor establish a fiduciary or similar relationship among the parties. The parties hereto acknowledge and agree that (i) Citibank and its Affiliates may at any time have multiple banking relationships with the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (ii) Citibank and its Affiliates may own and deal in any class of securities of the Company and its Affiliates and in ADSs, and may be engaged at any time in transactions in which parties adverse to the Company, the Holders, the Beneficial Owners or their respective Affiliates may have interests, (iii) the Depositary and its Affiliates may from time to time have in their possession non-public information about the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (iv) nothing contained in the Deposit Agreement shall (a) preclude Citibank or any of its Affiliates from engaging in such transactions or establishing or maintaining such relationships, or (b) obligate Citibank or any of its Affiliates to disclose such information, transactions or relationships, or to account for any profit made or payment received in such transactions or relationships, (v) the Depositary shall not be deemed to have knowledge of any information any other division of Citibank or any of its Affiliates may have about the Company, the Holders, the Beneficial Owners, or any of their respective Affiliates, and (vi) the Company, the Depositary, the Custodian and their respective agents and controlling persons may be subject to the laws and regulations of jurisdictions other than the U.S. and England and Wales, and the authority of courts and regulatory authorities of such other jurisdictions, and, consequently, the requirements and the limitations of such other laws and regulations, and the decisions and orders of such other courts and regulatory authorities, may affect the rights and obligations of the parties to the Deposit Agreement.

(27) **Governing Law / Waiver of Jury Trial**. The Deposit Agreement and the ADRs shall be interpreted in accordance with, and all rights hereunder and thereunder and provisions hereof and thereof shall be governed by, the laws of the State of New York applicable to contracts made and to be wholly performed in that State. Notwithstanding anything contained in the Deposit Agreement, any ADR or any present or future provisions of the laws of the State of New York, the rights of holders of Shares and of any other Deposited Securities and the obligations and duties of the Company in respect of the holders of Shares and other Deposited Securities, as such, shall be governed by the laws of England and Wales (or, if applicable, such other laws as may govern the Deposited Securities).

EACH OF THE PARTIES TO THE DEPOSIT AGREEMENT (INCLUDING, WITHOUT LIMITATION, EACH HOLDER AND BENEFICIAL OWNER) IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING AGAINST THE COMPANY AND/OR THE DEPOSITARY ARISING OUT OF, OR RELATING TO, THE DEPOSIT AGREEMENT, ANY ADR AND ANY TRANSACTIONS CONTEMPLATED THEREIN (WHETHER BASED ON CONTRACT, TORT, COMMON LAW OR OTHERWISE).

(ASSIGNMENT AND TRANSFER SIGNATURE LINES)

FOR VALUE RECEIVED, the undersigned Holder hereby sell(s), assign(s) and transfer(s) unto whose taxpayer identification number is and whose address including postal zip code is , the within ADR and all rights thereunder, hereby irrevocably constituting and appointing attorney-in-fact to transfer said ADR on the books of the Depositary with full power of substitution in the premises.

Dated:

Name: _____
By:
Title:

NOTICE: The signature of the Holder to this assignment must correspond with the name as written upon the face of the within instrument in every particular, without alteration or enlargement or any change whatsoever.

If the endorsement be executed by an attorney, executor, administrator, trustee or guardian, the person executing the endorsement must give his/her full title in such capacity and proper evidence of authority to act in such capacity, if not on file with the Depositary, must be forwarded with this ADR.

_____
SIGNATURE GUARANTEED

All endorsements or assignments of ADRs must be guaranteed by a member of a Medallion Signature Program approved by the Securities Transfer Association, Inc.

Legends

[The ADRs issued in respect of Partial Entitlement American Depositary Shares shall bear the following legend on the face of the ADR: "This ADR evidences ADSs representing 'partial entitlement' Shares of Orchard Therapeutics plc and as such do not entitle the holders thereof to the same per-share entitlement as other Shares (which are 'full entitlement' Shares) issued and outstanding at such time. The ADSs represented by this ADR shall entitle holders to distributions and entitlements identical to other ADSs when the Shares represented by such ADSs become 'full entitlement' Shares."]

EXHIBIT B

FEE SCHEDULE

ADS FEES AND RELATED CHARGES

All capitalized terms used but not otherwise defined herein shall have the meaning given to such terms in the Deposit Agreement.

I. ADS Fees

The following ADS fees are payable under the terms of the Deposit Agreement:

Service	Rate	By Whom Paid
(1) Issuance of ADSs (*e.g.*, an issuance upon a deposit of Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), excluding issuances as a result of distributions described in paragraph (4) below.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) issued.	Person for whom ADSs are issued.
(2) Cancellation of ADSs (*e.g.*, a cancellation of ADSs for Delivery of deposited Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) cancelled.	Person for whom ADSs are being cancelled.
(3) Distribution of cash dividends or other cash distributions (*e.g.*, upon a sale of rights and other entitlements).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
(4) Distribution of ADSs pursuant to (i) stock dividends or other free stock distributions, or (ii) an exercise of rights to purchase additional ADSs.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
(5) Distribution of securities other than ADSs or rights to purchase additional ADSs (*e.g.*, spin-off shares).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
(6) ADS Services.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held on the applicable record date(s) established by the Depositary.	Person holding ADSs on the applicable record date(s) established by the Depositary.

II. Charges

The Company, Holders, Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with ADS issuances and cancellations, and persons for whom ADSs are issued or cancelled shall be responsible for the following ADS charges under the terms of the Deposit Agreement:

(i) taxes (including applicable interest and penalties) and other governmental charges;

(ii) such registration fees as may from time to time be in effect for the registration of Shares or other Deposited Securities on the share register and applicable to transfers of Shares or other Deposited Securities to or from the name of the Custodian, the Depositary or any nominees upon the making of deposits and withdrawals, respectively;

(iii) such cable, telex and facsimile transmission and delivery expenses as are expressly provided in the Deposit Agreement to be at the expense of the person depositing Shares or withdrawing Deposited Property or of the Holders and Beneficial Owners of ADSs;

(iv) the expenses and charges incurred by the Depositary in the conversion of foreign currency (including transaction spreads);

(v) such fees and expenses as are incurred by the Depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to Deposited Property, ADSs and ADRs; and

(vi) the fees and expenses incurred by the Depositary, the Custodian, or any nominee in connection with the servicing or delivery of Deposited Property.

Goodwin Procter (UK) LLP
100 Cheapside
London EC2V 6DY

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+44 (0) 20 7447 4200

23 October 2018

Orchard Therapeutics plc
108 Cannon Street
London, EC4N 6EU

Ladies and Gentlemen:

Orchard Therapeutics plc – Registration Statement on Form F-1 – Exhibit 5.1

We have acted as English legal advisers to Orchard Therapeutics plc, a public limited company incorporated in England and Wales (the "**Company**") in connection with the proposed offering of American Depositary Shares (the "**ADSs**") representing ordinary shares of nominal value £0.10 each in the capital of the Company (the "**Ordinary Shares**") (the "**Offering**" and the Ordinary Shares allotted and issued in connection therewith to Citibank N.A. as the custodian and represented by ADSs, being the "**Shares**"). Each ADS represents one Ordinary Share of the Company.

1. INTRODUCTION

1.1 Purpose

In connection with the preparation and filing of a registration statement on Form F-1 (File No.333-227698) (such registration statement, as amended through the date hereof, the "**Registration Statement**"), to which this letter is attached as an exhibit, with the U.S. Securities and Exchange Commission (the "**SEC**") pursuant to the U.S. Securities Act of 1933, as amended (the "**Securities Act**"), we have been asked to provide opinions on certain matters, as set out below. We have taken instruction in this regard solely from the Company.

1.2 Defined terms and headings

In this letter:

(a) capitalised terms used without definition in this letter or the schedules hereto have the meanings assigned to them in the Registration Statement unless a contrary indication appears;

(b) headings are for ease of reference only and shall not affect interpretation; and

(c) the term "**Shares**" shall include any additional ADSs registered by the Company pursuant to Rule 462(b) under the Securities Act in connection with the Offering contemplated by the Registration Statement.

1.3 **Legal review**

For the purpose of issuing this letter, we have examined such questions of law as we have considered appropriate. We have reviewed only the following documents and conducted only the following enquiries and searches:

(a) an online search at Companies House in respect of information available for inspection on the Company's file conducted on 23 October 2018 at 10.30 a.m. (London time);

(b) an enquiry of the Central Index of Winding Up Petitions, London on 23 October 2018 at 10.30 a.m. (London time) ((a) and (b) together, the "**Searches**");

(c) a PDF copy of the written resolutions passed by the shareholders of the Company in connection with the Offering (the "**Written Resolutions**");

(d) draft minutes of a meeting of the board of directors of Orchard Therapeutics Limited held on 25 September 2018 at which it was resolved, inter alia, to appoint a pricing committee of the board of directors of the Company;

(e) a PDF copy of the written resolutions of the board of directors of the Company at which it was resolved, inter alia, to allot the Shares (the "**Allotment Resolutions**" and together with the Written Resolutions, the "**Corporate Approvals**");

(f) a PDF executed copy of a letter from shareholders in the Company comprising an "Investor Consent" (as defined in the Company's articles of association in effect for the time being) dated 18 October 2018 approving, amongst other things, the conversion of all class of shares in the Company into a single class of ordinary shares (the "**Investor Consent**");

(g) a PDF copy of the current articles of association of the Company dated 10 October 2018 (the "**Current Articles**") and a certificate of incorporation of the Company dated 1 August 2018;

(h) a draft copy of the articles of association of the Company to be adopted conditional on the completion of the Offering pursuant to a special resolution passed as part of the Written Resolutions (the "**IPO Articles**"); and

(i) a copy of the Registration Statement, as amended.

1.4 **Applicable law**

This letter, the opinions given in it, and any non-contractual obligations arising out of or in connection with this letter and/or the opinions given in it, are governed by, and to be construed in accordance with, English law and relate only to English law as applied by the English courts, including the laws of the European Union to the extent having the force of law in England, as at today's date. In particular:

(a) we have not investigated the laws of any country other than England and we express no opinion in this letter on the laws of any jurisdiction other than England and we assume that no foreign law affects any of the opinions given below. It is assumed that no foreign law which may apply to the matters contemplated by the Registration Statement, the Offering, the Company, any document or any other matter contemplated by any document would or might affect this letter and/or the opinions given in it.

(b) we do not undertake or accept any obligation to update this letter and/or the opinions given in it to reflect subsequent changes in English law or factual matters, and

1.5 **Assumptions and reservations**

The opinions given in this letter are given on the basis of each of the assumptions set out in paragraph 1.4, schedule 1 (*Assumptions*) and are subject to each of the reservations set out in schedule 2 (*Reservations*) to this letter. The opinions given in this letter are strictly limited to the matters stated in paragraph 2 (*Opinions*) below and do not extend, and should not be read as extending, by implication or otherwise, to any other matters.

2. OPINION

Subject to paragraph 1 (*Introduction*) and the other matters set out in this letter and its schedules, and subject further to the following:

(a) the Registration Statement becoming effective under the Securities Act;

(b) the number of Shares to be allotted and issued in connection with the Offering not being greater than 15,333,332 and such Shares being allotted and issued by 31 December 2018;

(c) that the Corporate Approvals were or will be (as appropriate) each passed at a meeting which was or will be duly convened and held in accordance with all applicable laws and regulations; that in particular, but without limitation, a duly qualified quorum of directors or, as the case may be, shareholders was or will be present in each case throughout the meeting and voted in favour of the resolutions; and that in relation to each meeting of the board of directors of the Company and of the Committee, each provision contained in the Companies Act 2006, as amended (the "**Act**") or the Current Articles relating to the declaration of the directors' interests or the power of the interested directors to vote and to count in the quorum was or will be duly observed;

(d) the receipt in full of payment for the Shares in an amount of "cash consideration" (as defined in section 583(3) of the Act) of not less than the aggregate nominal value for such Shares; and

(e) valid entries having been made in relation to the allotment and issue of the Shares in the books and registers of the Company,

it is our opinion that, as at today's date, the Shares, if and when allotted and issued, registered in the name of the recipient in the register of members of the Company and delivered as described in the Registration Statement, will be duly and validly authorised and issued, fully paid or credited as fully paid (subject to the receipt of valid consideration by the Company for the issue thereof in connection with the Offering) and will not be subject to any call for payment of further capital.

3. EXTENT OF OPINIONS

We express no opinion as to any agreement, instrument or other document other than as specified in this letter or as to any liability to tax or duty which may arise or be suffered as a result of or in connection with the Offering or the transactions contemplated thereby.

This letter only applies to those facts and circumstances which exist as at today's date and we assume no obligation or responsibility to update or supplement this letter to reflect any facts or circumstances which may subsequently come to our attention, any changes in laws which may occur after today, or to inform the addressee of any change in circumstances happening after the date of this letter which would alter our opinion.

4. DISCLOSURE AND RELIANCE

This letter is addressed to you in connection with the Registration Statement. We consent to the filing of this letter as an exhibit to the Registration Statement. We further consent to the incorporation by reference of this letter and consent into any registration statement filed pursuant to Rule 462(b) under the Securities Act with respect to the Shares. In giving such consent, we do not thereby admit that we are in the category of persons whose consent is required under Section 7 of the Securities Act or the rules and regulations thereunder.

Other than for the purpose set out in the prior paragraph, this letter may not be relied upon, or assigned, for any purpose, without our prior written consent, which may be granted or withheld in our discretion.

Yours faithfully

/s/ Goodwin Procter (UK) LLP

Goodwin Procter (UK) LLP

SCHEDULE 1

ASSUMPTIONS

The opinions in this letter have been given on the basis of the following assumptions:

(a) the genuineness of all signatures, stamps and seals on all documents, the authenticity and completeness of all documents submitted to us as originals, and the conformity to original documents of all documents submitted to us as copies;

(b) that, where a document has been examined by us in draft or specimen form, it will be or has been duly executed in the form of that draft or specimen, and that each of the signed documents examined by us has been duly executed and, where applicable, delivered on behalf of the Company;

(c) that the articles of association of the Company referred to in paragraph 1.3(g) of this letter remain in full force and effect, and, save for the adoption of the IPO Articles upon the Offering, no alteration has been made or will be made to such articles of association, in each case prior to the date of allotment and issue of the Shares (the "Allotment Date");

(d) on the Allotment Date the Company will comply with all applicable laws to allot and issue the Shares and the Company will receive such amounts as are necessary to fully pay the nominal value of the Shares and any applicable share premium;

(e) that all documents, forms and notices which should have been delivered to the Registrar of Companies in respect of the Company have been so delivered, that information revealed by the Searches was complete and accurate in all respects and has not, since the time of the Searches, been altered and that the results of the Searches will remain complete and accurate as at the Allotment Date;

(f) that the Company has not taken any corporate or other action nor have any steps been taken or legal proceedings been started against the Company for the liquidation, winding up, dissolution, reorganisation or bankruptcy of, or for the appointment of a liquidator, receiver, trustee, administrator, administrative receiver or similar officer of, the Company or all or any of its assets (or any analogous proceedings in any jurisdiction) and the Company is not unable to pay its debts as they fall due within the meaning of section 123 of the Insolvency Act 1986, as amended, and will not become unable to pay its debts within the meaning of that section as a result of any of the transactions contemplated herein, is not insolvent and has not been dissolved or declared bankrupt;

(g) that the minutes of the meetings of the board of directors of the Company provided to us in connection with the giving of the opinions in this letter reflect a true record of the proceedings described in them in duly convened, constituted and quorate meetings in which all constitutional, statutory and other formalities were duly observed, and the resolutions set out in the minutes were validly passed and have not been and will not be revoked or varied and remain in full force and effect and will remain so as at the Allotment Date;

(h) that the resolutions set out in the Written Resolutions were validly passed and have not been and will not be revoked or varied and remain in full force and effect and will remain so as at the Allotment Date;

(i) that in relation to the allotment and issue of the Shares, the directors of the Company have acted and will act in the manner required by section 172 of the Act (Duty to promote the success of the Company), and there has not been and will not be any bad faith, breach of trust, fraud, coercion, duress or undue influence on the part of any of the directors of the Company;

(j) following the date of this letter and prior to the issue of the Ordinary Shares, the Company will validly enter into an underwriting agreement on substantially the terms and conditions described in Exhibit 1.1 of the Registration Statement;

(k) that no Shares or rights to subscribe for Shares have been or shall be offered to the public in the United Kingdom in breach of the Financial Services and Markets Act 2000, as amended ("FSMA") or of any other United Kingdom laws or regulations concerning offers of securities to the public, and no communication has been or shall be made in relation to the Shares in breach of section 21 of FSMA or any other United Kingdom laws or regulations relating to offers or invitations to subscribe for, or to acquire rights to subscribe for or otherwise acquire, shares or other securities; and

(l) the Company is not, nor will be, engaging in criminal, misleading, deceptive or unconscionable conduct or seeking to conduct any relevant transaction or any associated activity in a manner or for a purpose which might render any transaction contemplated under the Corporate Approvals or any associated activity illegal, void or voidable.

SCHEDULE 2

RESERVATIONS

The opinions in this letter are subject to the following reservations:

(a) the Searches are not capable of revealing conclusively whether or not a winding-up or administration petition or order has been presented or made, a receiver appointed, a company voluntary arrangement proposed or approved or any other insolvency proceeding commenced, and the available records may not be complete or up-to-date. In particular, the Central Registry of Winding-Up Petitions in England may not contain details of administration applications filed, or appointments recorded in or orders made by, district registries and county courts outside London. Searches at Companies House and at the Central Registry of Winding Up Petitions in England are not capable of revealing whether or not a winding up petition or a petition for the making of an administration order has been presented and, further, notice of a winding up order or resolution, notice of an administration order and notice of the appointment of a receiver may not be filed at Companies House immediately and there may be a delay in the relevant notice appearing on the file of the company concerned. Further, not all security interests are registrable, such security interests have not in fact been registered or such security interests have been created by an individual or an entity which is not registered in England. We have not made enquiries of any District Registry or County Court in England;

(b) the opinions set out in this letter are subject to: (i) any limitations arising from applicable laws relating to insolvency, bankruptcy, administration, reorganisation, liquidation, moratoria, schemes or analogous circumstances; and (ii) an English court exercising its discretion under section 426 of the Insolvency Act 1986 (*co-operation between courts exercising jurisdiction in relation to insolvency*) to assist the courts having the corresponding jurisdiction in any part of the United Kingdom or any relevant country or territory;

(c) we express no opinion as to matters of fact;

(d) we have only reviewed the documents listed in paragraph 2 (*Opinion*) above;

(e) we have made no enquiries of any individual connected with the Company;

(f) a certificate, documentation, notification, opinion or the like might be held by the English courts not to be conclusive if it can be shown to have an unreasonable or arbitrary basis or in the event of a manifest error; and

(g) it should be understood that we have not been responsible for investigating or verifying (i) the accuracy of the facts, including statements of foreign law, or the reasonableness of any statements of opinion, contained in the Registration Statement; or (ii) that no material facts have been omitted from it.

ORCHARD THERAPEUTICS PLC

2018 SHARE OPTION AND INCENTIVE PLAN

SECTION 1. GENERAL PURPOSE OF THE PLAN; DEFINITIONS

The name of the plan is the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "**Plan**"). The purpose of the Plan is to encourage and enable the officers, employees, Non-Employee Directors and Consultants of Orchard Therapeutics plc (the "**Company**") and its Affiliates upon whose judgment, initiative and efforts the Company largely depends for the successful conduct of its businesses to acquire a proprietary interest in the Company. It is anticipated that providing such persons with a direct stake in the Company's welfare will assure a closer identification of their interests with those of the Company and its shareholders, thereby stimulating their efforts on the Company's behalf and strengthening their desire to remain with the Company.

The following terms shall be defined as set forth below:

"Administrator" means either the Board or the remuneration committee of the Board or a similar committee performing the functions of the remuneration committee and which is comprised of not less than two Non-Employee Directors who are independent.

"*ADSs"* means American Depositary Shares, representing Ordinary Shares on deposit with a U.S. banking institution selected by the Company.

"*Affiliate*" means, at the time of determination, any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 of the U.S. Securities Act. The Board will have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition.

"Award" or *"Awards,"* except where referring to a particular category of grant under the Plan, shall include Incentive Share Options, Non-Qualified Share Options, Share Appreciation Rights, Restricted Share Units, Restricted Share Awards, Unrestricted Share Awards, Cash-Based Awards, and Dividend Equivalent Rights.

"*Award Certificate"* means a written or electronic document setting forth the terms and provisions applicable to an Award granted under the Plan. Each Award Certificate is subject to the terms and conditions of the Plan.

"Board" means the Board of Directors of the Company.

"Cash-Based Award" means an Award entitling the recipient to receive a cash-denominated payment.

"*Consultant"* means a consultant or adviser who provides *bona fide* services to the Company or an Affiliate as an independent contractor and who qualifies as a consultant or advisor under Instruction A.1.(a)(1) of Form S-8 under the U.S. Securities Act.

"*Dividend Equivalent Right*" means an Award entitling the grantee to receive credits based on cash dividends that would have been paid on the Shares specified in the Dividend Equivalent Right (or other award to which it relates) if such shares had been issued to and held by the grantee.

"*Effective Date*" means the date on which the Plan becomes effective as set forth in Section 21.

"*Fair Market Value*" of the Shares on any given date means the fair market value of the Shares determined in good faith by the Administrator; provided, however, that if the ADSs are listed on the National Association of Securities Dealers Automated Quotation System ("**NASDAQ**"), NASDAQ Global Market, The New York Share Exchange or another national securities exchange or traded on any established market, the determination shall be made by reference to market quotations. If there are no market quotations for such date, the determination shall be made by reference to the last date preceding such date for which there are market quotations; provided further, however, that if the date for which Fair Market Value is determined is the Registration Date, the Fair Market Value shall be the "Price to the Public" (or equivalent) set forth on the cover page for the final prospectus relating to the Company's initial public offering.

"*Incentive Share Option*" means any Share Option designated and qualified as an "incentive stock option" as defined in Section 422 of the U.S. Code.

"*Non-Employee Director*" means a member of the Board who is not also an employee of the Company or any Subsidiary.

"*Non-Qualified Share Option*" means any Share Option that is not an Incentive Share Option.

"*Option*" or "*Share Option*" means any option to purchase Shares granted pursuant to Section 5.

"*Ordinary Shares*" mean ordinary shares in the Company, with a nominal value of £0.00001 per share, subject to adjustments pursuant to Section 3.

"*Registration Date*" means the date upon which the registration statement on Form S-1 that is filed by the Company with respect to its initial public offering is declared effective by the Securities and Exchange Commission.

"*Restricted Shares*" means the Shares underlying a Restricted Share Award that remain subject to a risk of forfeiture or the Company's right of repurchase.

"*Restricted Share Award*" means an Award of Restricted Shares subject to such restrictions and conditions as the Administrator may determine at the time of grant.

"*Restricted Share Units*" means an Award of Share units subject to such restrictions and conditions as the Administrator may determine at the time of grant.

"*Sale Event*" shall mean (i) the sale of all or substantially all of the assets of the Company on a consolidated basis to an unrelated person or entity, (ii) a merger, reorganization or consolidation pursuant to which the holders of the Company's outstanding voting power and outstanding Share immediately prior to such transaction do not own a majority of the outstanding voting power and outstanding Share or other equity interests of the resulting or successor entity (or its ultimate parent, if applicable) immediately upon completion of such transaction, (iii) the sale of all of the Share of the Company to an unrelated person, entity or group thereof acting in concert, or (iv) any other transaction in which the owners of the Company's outstanding voting power immediately prior to such transaction do not own at least a majority of the outstanding voting power of the Company or any successor entity immediately upon completion of the transaction other than as a result of the acquisition of securities directly from the Company.

"*Sale Price*" means the value as determined by the Administrator of the consideration payable, or otherwise to be received by shareholders, per Share pursuant to a Sale Event.

"*Section 409A*" means Section 409A of the U.S. Code and the regulations and other guidance promulgated thereunder.

"*Share*" means an Ordinary Share and/or the number of ADSs equal to an Ordinary Share, as the context may require.

"*Share Appreciation Right*" means an Award entitling the recipient to receive Shares (or cash, to the extent explicitly provided for in the applicable Award Certificate) having a value equal to the excess of the Fair Market Value of the Share on the date of exercise over the exercise price of the Share Appreciation Right multiplied by the number of Shares with respect to which the Share Appreciation Right shall have been exercised.

"*Subsidiary*" means any corporation or other entity (other than the Company) in which the Company has at least a 50 percent interest, either directly or indirectly.

"*Ten Percent Owner*" means an employee who owns or is deemed to own (by reason of the attribution rules of Section 424(d) of the U.S. Code) more than 10 percent of the combined voting power of all classes of Share of the Company or any parent or subsidiary corporation.

"*Unrestricted Share Award*" means an Award of Shares free of any restrictions.

"*U.S. Code*" means the Internal Revenue Code of 1986, as amended, and any successor Code, and related rules, regulations and interpretations.

"*U.S. Exchange Act*" means the Securities Exchange Act of 1934, as amended, and the rules and regulations thereunder.

"*U.S. Securities Act*" means the U.S. Securities Act of 1933, as amended, and the rules and regulations thereunder.

SECTION 2. ADMINISTRATION OF PLAN; ADMINISTRATOR AUTHORITY TO SELECT GRANTEES AND DETERMINE AWARDS

(a) Administration of Plan. The Plan shall be administered by the Administrator.

(b) Powers of Administrator. The Administrator shall have the power and authority to grant Awards consistent with the terms of the Plan, including the power and authority:

(i) to select the individuals to whom Awards may from time to time be granted;

(ii) to determine the time or times of grant, and the extent, if any, of Incentive Share Options, Non-Qualified Share Options, Share Appreciation Rights, Restricted Share Awards, Restricted Share Units, Unrestricted Share Awards, Cash-Based Awards, and Dividend Equivalent Rights, or any combination of the foregoing, granted to any one or more grantees;

(iii) to determine the number of Shares to be covered by any Award;

(iv) to determine and modify from time to time the terms and conditions, including restrictions, not inconsistent with the terms of the Plan, of any Award, which terms and conditions may differ among individual Awards and grantees, and to approve the forms of Award Certificates;

(v) to accelerate at any time the exercisability or vesting of all or any portion of any Award;

(vi) subject to the provisions of Section 5(c), to extend at any time the period in which Share Options may be exercised; and

(vii) at any time to adopt, alter and repeal such rules, guidelines and practices for administration of the Plan and for its own acts and proceedings as it shall deem advisable; to interpret the terms and provisions of the Plan and any Award (including related written instruments); to make all determinations it deems advisable for the administration of the Plan; to decide all disputes arising in connection with the Plan; and to otherwise supervise the administration of the Plan.

All decisions and interpretations of the Administrator shall be binding on all persons, including the Company and Plan grantees.

(c) Delegation of Authority to Grant Awards. Subject to applicable law, the Administrator, in its discretion, may delegate to a committee consisting of one or more officers of the Company all or part of the Administrator's authority and duties with respect to the granting of Awards to individuals who are (i) not subject to the reporting and other provisions of Section 16 of the U.S. Exchange Act, as applicable, and (ii) not members of the delegated committee. Any such delegation by the Administrator shall include a limitation as to the amount of Share underlying Awards that may be granted during the period of the delegation and shall contain guidelines as to the determination of the exercise price and the vesting criteria. The Administrator may revoke or amend the terms of a delegation at any time but such action shall

not invalidate any prior actions of the Administrator's delegate or delegates that were consistent with the terms of the Plan.

(d) Award Certificate. Awards under the Plan shall be evidenced by Award Certificates that set forth the terms, conditions and limitations for each Award which may include, without limitation, the term of an Award and the provisions applicable in the event employment or service terminates.

(e) Indemnification. Neither the Board nor the Administrator, nor any member of either or any delegate thereof, shall be liable for any act, omission, interpretation, construction or determination made in good faith in connection with the Plan, and the members of the Board and the Administrator (and any delegate thereof) shall be entitled in all cases to indemnification and reimbursement by the Company in respect of any claim, loss, damage or expense (including, without limitation, reasonable attorneys' fees) arising or resulting therefrom to the fullest extent permitted by law and/or under the Company's articles or bylaws or any directors' and officers' liability insurance coverage which may be in effect from time to time and/or any indemnification agreement between such individual and the Company.

(f) Foreign Award Recipients. Notwithstanding any provision of the Plan to the contrary, in order to comply with the laws in other countries in which the Company and its Subsidiaries operate or have employees or other individuals eligible for Awards, the Administrator, in its sole discretion, shall have the power and authority to: (i) determine which Subsidiaries shall be covered by the Plan; (ii) determine which individuals outside the United States are eligible to participate in the Plan; (iii) modify the terms and conditions of any Award granted to individuals outside the United States to comply with applicable foreign laws; (iv) establish subplans and modify exercise procedures and other terms and procedures, to the extent the Administrator determines such actions to be necessary or advisable (and such subplans and/or modifications shall be attached to this Plan as appendices); provided, however, that no such subplans and/or modifications shall increase the share limitations contained in Section 3(a) hereof; and (v) take any action, before or after an Award is made, that the Administrator determines to be necessary or advisable to obtain approval or comply with any local governmental regulatory exemptions or approvals. Notwithstanding the foregoing, the Administrator may not take any actions hereunder, and no Awards shall be granted, that would violate the U.S. Exchange Act or any other applicable United States securities law, the U.S. Code, or any other applicable United States governing statute or law.

SECTION 3. SHARES ISSUABLE UNDER THE PLAN; MERGERS; SUBSTITUTION

(a) Shares Issuable. The maximum number of Shares reserved and available for issuance under the Plan shall be 4,247,023 Shares (the "**Initial Limit**"), subject to adjustment as provided in Section 3(b), plus on January 1, 2019 and each January 1 thereafter, the number of Shares reserved and available for issuance under the Plan shall be cumulatively increased by five percent (5%) of the number of Shares issued and outstanding on the immediately preceding December 31, or such lesser number as the Administrator may determine (the "**Annual Increase**"). Subject to such overall limitation, the maximum aggregate number of Shares that may be issued in the form of Incentive Share Options shall not exceed the Initial Limit cumulatively increased on January 1, 2019 and on each January 1 thereafter by the lesser of the

Annual Increase for such year or 4,247,023 Shares, subject in all cases to adjustment as provided in Section 3(b). For purposes of this limitation, the Shares underlying any awards under Plan or the Orchard Therapeutics plc 2016 Employee Share Option Plan that are forfeited, canceled, held back upon exercise of an Option or settlement of an Award to cover the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of Shares or otherwise terminated (other than by exercise) shall be added back to the Shares available for issuance under the Plan and, to the extent permitted under Section 422 of the U.S. Code and the regulations promulgated thereunder, the Shares that may be issued as Incentive Share Options. In the event the Company repurchases Shares on the open market, such Shares shall not be added to the Shares available for issuance under the Plan. Subject to such overall limitations, Shares may be issued up to such maximum number pursuant to any type or types of Award. The shares available for issuance under the Plan may be authorized but unissued Shares or Shares reacquired by the Company.

(b) Changes in Shares. Subject to Section 3(c) hereof, if, as a result of any reorganization, recapitalization, reclassification, share dividend, share split, reverse share split or other similar change in the Company's capital shares, the outstanding Shares are increased or decreased or are exchanged for a different number or kind of shares or other securities of the Company, or additional shares or new or different shares or other securities of the Company or other non-cash assets are distributed with respect to such Shares or other securities, or, if, as a result of any merger or consolidation, sale of all or substantially all of the assets of the Company, the outstanding Shares are converted into or exchanged for securities of the Company or any successor entity (or a parent or subsidiary thereof), the Administrator shall make an appropriate or proportionate adjustment in (i) the maximum number of shares reserved for issuance under the Plan, including the maximum number of shares that may be issued in the form of Incentive Share Options, (ii) the number and kind of shares or other securities subject to any then outstanding Awards under the Plan, (iii) the repurchase price, if any, per share subject to each outstanding Restricted Share Award, and (iv) the exercise price for each share subject to any then outstanding Share Options and Share Appreciation Rights under the Plan, without changing the aggregate exercise price (i.e., the exercise price multiplied by the number of Share Options and Share Appreciation Rights) as to which such Share Options and Share Appreciation Rights remain exercisable. The Administrator shall also make equitable or proportionate adjustments in the number of shares subject to outstanding Awards and the exercise price and the terms of outstanding Awards to take into consideration cash dividends paid other than in the ordinary course or any other extraordinary corporate event. The adjustment by the Administrator shall be final, binding and conclusive. No fractional Shares shall be issued under the Plan resulting from any such adjustment, but the Administrator in its discretion may make a cash payment in lieu of fractional shares.

(c) Mergers and Other Transactions. In the case of and subject to the consummation of a Sale Event, the parties thereto may cause the assumption or continuation of Awards theretofore granted by the successor entity, or the substitution of such Awards with new Awards of the successor entity or parent thereof, with appropriate adjustment as to the number and kind of shares and, if appropriate, the per share exercise prices, as such parties shall agree. To the extent the parties to such Sale Event do not provide for the assumption, continuation or substitution of Awards, upon the effective time of the Sale Event, the Plan and all outstanding Awards granted hereunder shall terminate. In such case, except as may be otherwise provided in

the relevant Award Certificate, all Options and Share Appreciation Rights that are not exercisable immediately prior to the effective time of the Sale Event shall become fully exercisable as of the effective time of the Sale Event, all other Awards with time-based vesting, conditions or restrictions shall become fully vested and nonforfeitable as of the effective time of the Sale Event, and all Awards with conditions and restrictions relating to the attainment of performance goals may become vested and nonforfeitable in connection with a Sale Event in the Administrator's discretion or to the extent specified in the relevant Award Certificate. In the event of such termination, (i) the Company shall have the option (in its sole discretion) to make or provide for a payment, in cash or in kind, to the grantees holding Options and Share Appreciation Rights, in exchange for the cancellation thereof, in an amount equal to the difference between (A) the Sale Price multiplied by the number of Shares subject to outstanding Options and Share Appreciation Rights (to the extent then exercisable at prices not in excess of the Sale Price) and (B) the aggregate exercise price of all such outstanding Options and Share Appreciation Rights (provided that, in the case of an Option or Share Appreciation Right with an exercise price equal to or less than the Sale Price, such Option or Share Appreciation Right shall be cancelled for no consideration); or (ii) each grantee shall be permitted, within a specified period of time prior to the consummation of the Sale Event as determined by the Administrator, to exercise all outstanding Options and Share Appreciation Rights (to the extent then exercisable) held by such grantee. The Company shall also have the option (in its sole discretion) to make or provide for a payment, in cash or in kind, to the grantees holding other Awards in an amount equal to the Sale Price multiplied by the number of vested Shares under such Awards.

SECTION 4. ELIGIBILITY

Grantees under the Plan will be such employees, Non-Employee Directors and Consultants of the Company and its Affiliates as are selected from time to time by the Administrator in its sole discretion; provided that Awards may not be granted to employees, Directors and Consultants who are providing services only to any "parent" of the Company, as such term is defined in Rule 405 of the U.S. Securities Act, unless (i) the Shares underlying the Awards is treated as "service recipient stock" under Section 409A or (ii) the Company, in consultation with its legal counsel, has determined that such Awards are exempt from or otherwise comply with Section 409A.

SECTION 5. SHARE OPTIONS

(a) Award of Share Options. The Administrator may grant Share Options under the Plan. Any Share Option granted under the Plan shall be in such form as the Administrator may from time to time approve.

Share Options granted under the Plan may be either Incentive Share Options or Non-Qualified Share Options. Incentive Share Options may be granted only to employees of the Company or any Subsidiary that is a "subsidiary corporation" within the meaning of Section 424(f) of the U.S. Code. To the extent that any Option does not qualify as an Incentive Share Option, it shall be deemed a Non-Qualified Share Option.

Share Options granted pursuant to this Section 5 shall be subject to the following terms and conditions and shall contain such additional terms and conditions, not inconsistent with the terms of the Plan, as the Administrator shall deem desirable. If the Administrator so determines, Share Options may be granted in lieu of cash compensation at the optionee's election, subject to such terms and conditions as the Administrator may establish.

(b) Exercise Price. The exercise price per Share covered by a Share Option granted pursuant to this Section 5 shall be determined by the Administrator at the time of grant but shall not be less than 100 percent of the Fair Market Value on the date of grant. In the case of an Incentive Share Option that is granted to a Ten Percent Owner, the option price of such Incentive Share Option shall be not less than 110 percent of the Fair Market Value on the grant date. Notwithstanding the foregoing, Share Options may be granted with an exercise price per share that is less than 100 percent of the Fair Market Value on the date of grant (i) pursuant to a transaction described in, and in a manner consistent with, Section 424(a) of the U.S. Code or (ii) to individuals who are not subject to U.S. income tax.

(c) Option Term. The term of each Share Option shall be fixed by the Administrator, but no Share Option shall be exercisable more than ten years after the date the Share Option is granted. In the case of an Incentive Share Option that is granted to a Ten Percent Owner, the term of such Share Option shall be no more than five years from the date of grant.

(d) Exercisability; Rights of a Shareholder. Share Options shall become exercisable at such time or times, whether or not in installments, as shall be determined by the Administrator at or after the grant date. The Administrator may at any time accelerate the exercisability of all or any portion of any Share Option. An optionee shall have the rights of a shareholder only as to shares acquired upon the exercise of a Share Option and not as to unexercised Share Options.

(e) Method of Exercise. Share Options may be exercised in whole or in part, by giving written or electronic notice of exercise to the Company, specifying the number of shares to be purchased. Payment of the purchase price may be made by one or more of the following methods except to the extent otherwise provided in the Option Award Certificate:

(i) In cash, by certified or bank check or other instrument acceptable to the Administrator;

(ii) Through the delivery (or attestation to the ownership following such procedures as the Company may prescribe) of Shares that are not then subject to restrictions under any Company plan. Such surrendered shares shall be valued at Fair Market Value on the exercise date;

(iii) By the optionee delivering to the Company a properly executed exercise notice together with irrevocable instructions to a broker to promptly deliver to the Company cash or a check payable and acceptable to the Company for the purchase price; provided that in the event the optionee chooses to pay the purchase price as so provided, the optionee and the broker shall comply with such procedures and enter into such agreements of indemnity and other agreements as the Company shall prescribe as a condition of such payment procedure; or

(iv) With respect to Share Options that are not Incentive Share Options, by a "net exercise" arrangement pursuant to which the Company will reduce the number of Shares issuable upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price.

Payment instruments will be received subject to collection. The transfer to the optionee on the records of the Company or of the transfer agent of the Shares to be purchased pursuant to the exercise of a Share Option will be contingent upon receipt from the optionee (or a purchaser acting in his stead in accordance with the provisions of the Share Option) by the Company of the full purchase price for such shares and the fulfillment of any other requirements contained in the Option Award Certificate or applicable provisions of laws (including the satisfaction of any withholding taxes that the Company is obligated to withhold with respect to the optionee). In the event an optionee chooses to pay the purchase price by previously-owned Shares through the attestation method, the number of Shares transferred to the optionee upon the exercise of the Share Option shall be net of the number of attested shares. In the event that the Company establishes, for itself or using the services of a third party, an automated system for the exercise of Share Options, such as a system using an internet website or interactive voice response, then the paperless exercise of Share Options may be permitted through the use of such an automated system.

(f) Annual Limit on Incentive Share Options. To the extent required for "incentive stock option" treatment under Section 422 of the U.S. Code, the aggregate Fair Market Value (determined as of the time of grant) of the Shares with respect to which Incentive Share Options granted under this Plan and any other plan of the Company or its parent and subsidiary corporations become exercisable for the first time by an optionee during any calendar year shall not exceed $100,000. To the extent that any Share Option exceeds this limit, it shall constitute a Non-Qualified Share Option.

SECTION 6. SHARE APPRECIATION RIGHTS

(a) Award of Share Appreciation Rights. The Administrator may grant Share Appreciation Rights under the Plan. A Share Appreciation Right is an Award entitling the recipient to receive Shares (or cash, to the extent explicitly provided for in the applicable Award Certificate) having a value equal to the excess of the Fair Market Value of a Share on the date of exercise over the exercise price of the Share Appreciation Right multiplied by the number of Shares with respect to which the Share Appreciation Right shall have been exercised.

(b) Exercise Price of Share Appreciation Rights. The exercise price of a Share Appreciation Right shall not be less than 100 percent of the Fair Market Value of the Share on the date of grant.

(c) Grant and Exercise of Share Appreciation Rights. Share Appreciation Rights may be granted by the Administrator independently of any Share Option granted pursuant to Section 5 of the Plan.

(d) Terms and Conditions of Share Appreciation Rights. Share Appreciation Rights shall be subject to such terms and conditions as shall be determined on the date of grant by the

Administrator. The term of a Share Appreciation Right may not exceed ten years. The terms and conditions of each such Award shall be determined by the Administrator, and such terms and conditions may differ among individual Awards and grantees.

SECTION 7. RESTRICTED SHARE AWARDS

(a) Nature of Restricted Share Awards. The Administrator may grant Restricted Share Awards under the Plan. A Restricted Share Award is any Award of Restricted Shares subject to such restrictions and conditions as the Administrator may determine at the time of grant. Conditions may be based on continuing employment (or other service relationship) and/or achievement of pre-established performance goals and objectives.

(b) Rights as a Shareholder. Upon the grant of the Restricted Share Award and payment of any applicable purchase price, a grantee shall have the rights of a shareholder with respect to the voting of the Restricted Shares and receipt of dividends; provided that if the lapse of restrictions with respect to the Restricted Share Award is tied to the attainment of performance goals, any dividends paid by the Company during the performance period shall accrue and shall not be paid to the grantee until and to the extent the performance goals are met with respect to the Restricted Share Award. Unless the Administrator shall otherwise determine, (i) uncertificated Restricted Shares shall be accompanied by a notation on the records of the Company or the transfer agent to the effect that they are subject to forfeiture until such Restricted Shares are vested as provided in Section 7(d) below, and (ii) certificated Restricted Shares shall remain in the possession of the Company until such Restricted Shares are vested as provided in Section 7(d) below, and the grantee shall be required, as a condition of the grant, to deliver to the Company such instruments of transfer as the Administrator may prescribe.

(c) Restrictions. Restricted Shares may not be sold, assigned, transferred, pledged or otherwise encumbered or disposed of except as specifically provided herein or in the Restricted Share Award Certificate. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, if a grantee's employment (or other service relationship) with the Company and its Subsidiaries terminates for any reason, any Restricted Shares that have not vested at the time of termination shall automatically and without any requirement of notice to such grantee from or other action by or on behalf of, the Company be deemed to have been reacquired by the Company at its original purchase price (if any) from such grantee or such grantee's legal representative simultaneously with such termination of employment (or other service relationship), and thereafter shall cease to represent any ownership of the Company by the grantee or rights of the grantee as a shareholder. Following such deemed reacquisition of Restricted Shares that are represented by physical certificates, a grantee shall surrender such certificates to the Company upon request without consideration.

(d) Vesting of Restricted Shares. The Administrator at the time of grant shall specify the date or dates and/or the attainment of pre-established performance goals, objectives and other conditions on which the non-transferability of the Restricted Shares and the Company's right of repurchase or forfeiture shall lapse. Subsequent to such date or dates and/or the attainment of such pre-established performance goals, objectives and other conditions, the shares on which all restrictions have lapsed shall no longer be Restricted Shares and shall be deemed "vested."

SECTION 8. RESTRICTED SHARE UNITS

(a) Nature of Restricted Share Units. The Administrator may grant Restricted Share Units under the Plan. A Restricted Share Unit is an Award of share units that may be settled in Shares (or cash, to the extent explicitly provided for in the Award Certificate) upon the satisfaction of such restrictions and conditions at the time of grant. Conditions may be based on continuing employment (or other service relationship) and/or achievement of pre-established performance goals and objectives. The terms and conditions of each such Award shall be determined by the Administrator, and such terms and conditions may differ among individual Awards and grantees. Except in the case of Restricted Share Units with a deferred settlement date that complies with Section 409A, at the end of the vesting period, the Restricted Share Units, to the extent vested, shall be settled in the form of Shares. Restricted Share Units with deferred settlement dates are subject to Section 409A and shall contain such additional terms and conditions as the Administrator shall determine in its sole discretion in order to comply with the requirements of Section 409A.

(b) Election to Receive Restricted Share Units in Lieu of Compensation. The Administrator may, in its sole discretion, permit a grantee to elect to receive a portion of future cash compensation otherwise due to such grantee in the form of an award of Restricted Share Units. Any such election shall be made in writing and shall be delivered to the Company no later than the date specified by the Administrator and in accordance with Section 409A and such other rules and procedures established by the Administrator. Any such future cash compensation that the grantee elects to defer shall be converted to a fixed number of Restricted Share Units based on the Fair Market Value of a Share on the date the compensation would otherwise have been paid to the grantee if such payment had not been deferred as provided herein. The Administrator shall have the sole right to determine whether and under what circumstances to permit such elections and to impose such limitations and other terms and conditions thereon as the Administrator deems appropriate. Any Restricted Share Units that are elected to be received in lieu of cash compensation shall be fully vested, unless otherwise provided in the Award Certificate.

(c) Rights as a Shareholder. A grantee shall have the rights as a shareholder only as to Shares acquired by the grantee upon settlement of Restricted Share Units; provided, however, that the grantee may be credited with Dividend Equivalent Rights with respect to the share units underlying his Restricted Share Units, subject to the provisions of Section 11 and such terms and conditions as the Administrator may determine.

(d) Termination. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, a grantee's right in all Restricted Share Units that have not vested shall automatically terminate upon the grantee's termination of employment (or cessation of service relationship) with the Company and its Subsidiaries for any reason.

SECTION 9. UNRESTRICTED SHARE AWARDS

Grant or Sale of Unrestricted Share. The Administrator may grant (or sell at par value or such higher purchase price determined by the Administrator) an Unrestricted Share Award under

the Plan. An Unrestricted Share Award is an Award pursuant to which the grantee may receive Shares of free of any restrictions under the Plan. Unrestricted Share Awards may be granted in respect of past services or other valid consideration, or in lieu of cash compensation due to such grantee.

SECTION 10. CASH-BASED AWARDS

Grant of Cash-Based Awards. The Administrator may grant Cash-Based Awards under the Plan. A Cash-Based Award is an Award that entitles the grantee to a payment in cash upon the attainment of specified performance goals. The Administrator shall determine the maximum duration of the Cash-Based Award, the amount of cash to which the Cash-Based Award pertains, the conditions upon which the Cash-Based Award shall become vested or payable, and such other provisions as the Administrator shall determine. Each Cash-Based Award shall specify a cash-denominated payment amount, formula or payment ranges as determined by the Administrator. Payment, if any, with respect to a Cash-Based Award shall be made in accordance with the terms of the Award and may be made in cash.

SECTION 11. DIVIDEND EQUIVALENT RIGHTS

(a) Dividend Equivalent Rights. The Administrator may grant Dividend Equivalent Rights under the Plan. A Dividend Equivalent Right is an Award entitling the grantee to receive credits based on cash dividends that would have been paid on the Shares specified in the Dividend Equivalent Right (or other Award to which it relates) if such shares had been issued to the grantee. A Dividend Equivalent Right may be granted hereunder to any grantee as a component of an award of Restricted Share Units or as a freestanding award. The terms and conditions of Dividend Equivalent Rights shall be specified in the Award Certificate. Dividend equivalents credited to the holder of a Dividend Equivalent Right may be paid currently or may be deemed to be reinvested in additional Shares, which may thereafter accrue additional equivalents. Any such reinvestment shall be at Fair Market Value on the date of reinvestment or such other price as may then apply under a dividend reinvestment plan sponsored by the Company, if any. Dividend Equivalent Rights may be settled in cash or Shares or a combination thereof, in a single installment or installments. A Dividend Equivalent Right granted as a component of an Award of Restricted Share Units shall provide that such Dividend Equivalent Right shall be settled only upon settlement or payment of, or lapse of restrictions on, such other Award, and that such Dividend Equivalent Right shall expire or be forfeited or annulled under the same conditions as such other Award.

(b) Termination. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, a grantee's rights in all Dividend Equivalent Rights shall automatically terminate upon the grantee's termination of employment (or cessation of service relationship) with the Company and its Subsidiaries for any reason.

SECTION 12. TRANSFERABILITY OF AWARDS

(a) Transferability. Except as provided in Section 12 (b) below, during a grantee's lifetime, his or her Awards shall be exercisable only by the grantee, by the grantee's legal

representative or guardian in the event of the grantee's incapacity (evidenced to the satisfaction of the Administrator) or the grantee's personal representatives in the case of his death. No Awards shall be sold, assigned, transferred or otherwise encumbered or disposed of by a grantee other than by will or by the laws of descent and distribution or pursuant to a domestic relations order. No Awards shall be subject, in whole or in part, to attachment, execution, or levy of any kind, and any purported transfer in violation hereof shall be null and void.

(b) Administrator Action. Notwithstanding Section 12(a), the Administrator, in its discretion, may provide either in the Award Certificate regarding a given Award or by subsequent written approval that the grantee (who is an employee or director) may transfer his or her Non-Qualified Share Options to his or her immediate family members, to trusts for the benefit of such family members, or to partnerships in which such family members are the only partners, provided that the transferee agrees in writing with the Company to be bound by all of the terms and conditions of this Plan and the applicable Award. In no event may an Award be transferred by a grantee for value.

(c) Family Member. For purposes of Section 12(b), "family member" shall mean a grantee's child, stepchild, grandchild, parent, stepparent, grandparent, spouse, former spouse, sibling, niece, nephew, mother-in-law, father-in-law, son-in-law, daughter-in-law, brother-in-law, or sister-in-law, including adoptive relationships, any person sharing the grantee's household (other than a tenant of the grantee), a trust in which these persons (or the grantee) have more than 50 percent of the beneficial interest, a foundation in which these persons (or the grantee) control the management of assets, and any other entity in which these persons (or the grantee) own more than 50 percent of the voting interests.

(d) Designation of Beneficiary. To the extent permitted by the Company, each grantee to whom an Award has been made under the Plan may designate a beneficiary or beneficiaries to exercise any Award or receive any payment under any Award payable on or after the grantee's death. Any such designation shall be on a form provided for that purpose by the Administrator and shall not be effective until received by the Administrator. If no beneficiary has been designated by a deceased grantee, or if the designated beneficiaries have predeceased the grantee, the beneficiary shall be the grantee's estate.

SECTION 13. TAX WITHHOLDING

(a) Payment by Grantee. If the Company or any Subsidiary is liable to account for tax (including Federal, state and local taxes and social security taxes in the US and their equivalent in any other jurisdiction) for which a grantee is liable by reason of the grant, release, exercise, assignment or surrender for consideration of an Award or the receipt of any benefit in connection with it, the Company and its Subsidiaries shall, to the extent permitted by the applicable law in the relevant jurisdiction, have the right to deduct any such taxes from any payment of any kind otherwise due to the grantee. The Company's obligation to deliver evidence of book entry (or share certificates) to any grantee is subject to and conditioned on tax withholding obligations being satisfied by the grantee.

(b) Payment in Shares. The Company's required tax withholding obligation may be satisfied, in whole or in part, by the Company withholding from Shares to be issued pursuant to

any Award a number of shares with an aggregate Fair Market Value (as of the date the withholding is effected) that would satisfy the withholding amount due; provided, however, that the amount withheld does not exceed the maximum statutory tax rate or such lesser amount as is necessary to avoid liability accounting treatment. The Administrator may also require Awards to be subject to mandatory share withholding up to the required withholding amount. For purposes of share withholding, the Fair Market Value of withheld shares shall be determined in the same manner as the value of Shares includible in income of the Participants. The required tax withholding obligation may also be satisfied, in whole or in part, by an arrangement whereby a certain number of Shares issued pursuant to any Award are immediately sold and proceeds from such sale are remitted to the Company in an amount that would satisfy the withholding amount due.

(c) UK national insurance contributions. At the request of the Company or Subsidiary by which the relevant grantee is employed at any time before the vesting or exercise of an Award which is a Share Option, the grantee must either agree to meet or elect, to the extent lawfully permitted (and in the case of an election, using a form approved by HM Revenue & Customs) that the whole of the liability for any secondary class 1 (employers') national insurance contributions arising as a result of the grant, release, exercise, assignment or surrender for consideration of the Share Option, shall be borne by or transferred to the grantee.

SECTION 14. SECTION 409A AWARDS

To the extent that any Award is determined to constitute "nonqualified deferred compensation" within the meaning of Section 409A (a "**409A Award**"), the Award shall be subject to such additional rules and requirements as specified by the Administrator from time to time in order to comply with Section 409A. In this regard, if any amount under a 409A Award is payable upon a "separation from service" (within the meaning of Section 409A) to a grantee who is then considered a "specified employee" (within the meaning of Section 409A), then no such payment shall be made prior to the date that is the earlier of (i) six months and one day after the grantee's separation from service, or (ii) the grantee's death, but only to the extent such delay is necessary to prevent such payment from being subject to interest, penalties and/or additional tax imposed pursuant to Section 409A. Further, the settlement of any 409A Award may not be accelerated except to the extent permitted by Section 409A.

SECTION 15. TERMINATION OF EMPLOYMENT, TRANSFER, LEAVE OF ABSENCE, ETC.

(a) Termination of Employment. If the grantee's employer ceases to be a Subsidiary, the grantee shall be deemed to have terminated employment for purposes of the Plan.

(b) For purposes of the Plan, the following events shall not be deemed a termination of employment:

(i) a transfer to the employment of the Company from a Subsidiary or from the Company to a Subsidiary, or from one Subsidiary to another; or

(ii) an approved leave of absence for military service or sickness, or for any other purpose approved by the Company, if the employee's right to re-employment is guaranteed

either by a statute or by contract or under the policy pursuant to which the leave of absence was granted or if the Administrator otherwise so provides in writing.

(c) In the case of grantees who are employed in the UK, the termination date of their employment shall be the date notice is given by or to them unless the Administrator decides that it can be a later date before the statutory or contractual expiry date of their notice period.

SECTION 16. AMENDMENTS AND TERMINATION

The Board may, at any time, amend or discontinue the Plan and the Administrator may, at any time, amend or cancel any outstanding Award for the purpose of satisfying changes in law or for any other lawful purpose, but no such action shall adversely affect rights under any outstanding Award without the holder's consent. The Administrator is specifically authorized to exercise its discretion to reduce the exercise price of outstanding Share Options or Share Appreciation Rights or effect the repricing of such Awards through cancellation and re-grants. To the extent required under the rules of any securities exchange or market system on which the Shares are listed, to the extent determined by the Administrator to be required by the U.S. Code to ensure that Incentive Share Options granted under the Plan are qualified under Section 422 of the U.S. Code, Plan amendments shall be subject to approval by the Company shareholders entitled to vote at a meeting of shareholders. Nothing in this Section 18 shall limit the Administrator's authority to take any action permitted pursuant to Section 3(b) or 3(c).

SECTION 17. STATUS OF PLAN

With respect to the portion of any Award that has not been exercised and any payments in cash, Shares or other consideration not received by a grantee, a grantee shall have no rights greater than those of a general creditor of the Company unless the Administrator shall otherwise expressly determine in connection with any Award or Awards. In its sole discretion, the Administrator may authorize the creation of trusts or other arrangements to meet the Company's obligations to deliver Shares or make payments with respect to Awards hereunder, provided that the existence of such trusts or other arrangements is consistent with the foregoing sentence.

SECTION 18. GENERAL PROVISIONS

(a) No Distribution. The Administrator may require each person acquiring Shares pursuant to an Award to represent to and agree with the Company in writing that such person is acquiring the shares without a view to distribution thereof.

(b) Issuance of Shares. To the extent certificated, Share certificates to grantees under this Plan shall be deemed delivered for all purposes when the Company or a transfer agent of the Company shall have mailed such certificates in the United States mail, addressed to the grantee, at the grantee's last known address on file with the Company. Uncertificated Shares shall be deemed delivered for all purposes when the Company or a transfer agent of the Company shall have given to the grantee by electronic mail (with proof of receipt) or by United States mail, addressed to the grantee, at the grantee's last known address on file with the Company, notice of issuance and recorded the issuance in its records (which may include electronic "book entry" records). Notwithstanding anything herein to the contrary, the Company shall not be required to issue or deliver any evidence of book entry or certificates evidencing Shares pursuant to the

exercise or settlement of any Award, unless and until the Administrator has determined, with advice of counsel (to the extent the Administrator deems such advice necessary or advisable), that the issuance and delivery is in compliance with all applicable laws, regulations of governmental authorities and, if applicable, the requirements of any exchange on which the Shares are listed, quoted or traded. Any Shares issued pursuant to the Plan shall be subject to any stop-transfer orders and other restrictions as the Administrator deems necessary or advisable to comply with federal, state or foreign jurisdiction, securities or other laws, rules and quotation system on which the Shares are listed, quoted or traded. The Administrator may place legends on any Share certificate or notations on any book entry to reference restrictions applicable to the Shares. In addition to the terms and conditions provided herein, the Administrator may require that an individual make such reasonable covenants, agreements, and representations as the Administrator, in its discretion, deems necessary or advisable in order to comply with any such laws, regulations, or requirements. The Administrator shall have the right to require any individual to comply with any timing or other restrictions with respect to the settlement or exercise of any Award, including a window-period limitation, as may be imposed in the discretion of the Administrator.

(c) Shareholder Rights. Until Shares are deemed delivered in accordance with Section 20(b), no right to vote or receive dividends or any other rights of a shareholder will exist with respect to Shares to be issued in connection with an Award, notwithstanding the exercise of a Share Option or any other action by the grantee with respect to an Award.

(d) Other Compensation Arrangements; No Employment Rights. Nothing contained in this Plan shall prevent the Board from adopting other or additional compensation arrangements, including trusts, and such arrangements may be either generally applicable or applicable only in specific cases. The adoption of this Plan and the grant of Awards do not confer upon any employee any right to continued employment with the Company or any Subsidiary. If a grantee ceases to be employed by the Company or any Subsidiary for any reason whatsoever (including as a result of being wrongfully or unfairly dismissed) they shall not be entitled, and by accepting an Award they shall be deemed to have waived any possible entitlement, to any sum or other benefit accrued or in prospect in connection with that Award, and no such loss or curtailment shall form part of any claim for damages for breach of the grantee's contract of employment or compensation for dismissal or any other claim whatsoever.

(e) Trading Policy Restrictions. Option exercises and other Awards under the Plan shall be subject to the Company's insider trading policies and procedures, as in effect from time to time.

(f) Clawback Policy. Awards under the Plan shall be subject to the Company's clawback policy, as in effect from time to time.

SECTION 19. EFFECTIVE DATE OF PLAN

This Plan shall become effective upon the date immediately preceding the Registration Date following shareholder approval in accordance with applicable law, the Company's bylaws and articles of incorporation, and applicable stock exchange rules. No grants of Share Options and other Awards may be made hereunder after the tenth anniversary of the Effective Date and

no grants of Incentive Share Options may be made hereunder after the tenth anniversary of the date the Plan is approved by the Board.

SECTION 20. GOVERNING LAW

This Plan and all Awards and actions taken thereunder shall be governed by, and construed in accordance with the law of England and Wales, applied without regard to conflict of law principles.

Exhibit 10.4

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "[***]". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT PURSUANT TO RULE 406 PROMULGATED UNDER THE SECURITIES ACT OF 1933, AS AMENDED.

5th April 2018

DEED OF NOVATION

between

GLAXO GROUP LIMITED

and

GLAXOSMITHKLINE RESEARCH & DEVELOPMENT LIMITED

and

GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED

and

GLAXOSMITHKLINE S.p.A.

and

FONDAZIONE TELETHON

and

OSPEDALE SAN RAFFAELE (IN ITS OWN CAPACITY AND AS SUCCESSOR IN INTEREST TO FONDAZIONE CENTRO SAN RAFFAELE DEL MONTE TABOR)

and

ORCHARD THERAPEUTICS LIMITED

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THIS DEED OF NOVATION is dated 5th April 2018

PARTIES

(1) **GLAXO GROUP LIMITED**, a company incorporated under the laws of England and Wales with company number [***] and registered offices at 980 Great West Road, Brentford, Middlesex, TW8 9GS ("**GGL**" or an "**Outgoing Party**");

(2) **GLAXOSMITHKLINE RESEARCH & DEVELOPMENT LIMITED**, a company incorporated under the laws of England and Wales with company number [***] and registered offices at 980 Great West Road, Brentford, Middlesex, TW8 9GS ("**GSK R&D**" or an "**Outgoing Party**");

(3) **GLAXOSMITHKLINE INTELLECTUAL PROPERTY DEVELOPMENT LIMITED**, a company incorporated under the laws of England and Wales with company number [***] and registered offices at 980 Great West Road, Brentford, Middlesex, TW8 9GS ("**GSK IPD**" or an "**Outgoing Party**");

(4) **GLAXOSMITHKLINE S.p.A.**, a private entity established under the laws of Italy with Tax ID and VAT Code [***] and registered offices at Via Fleming 2, 37100, Verona, Italy ("**GSK Italy**" or an "**Outgoing Party**");

(5) **FONDAZIONE TELETHON**, with registered offices at Via Varese 16b, 00185, Rome, Italy ("**Telethon**" or a "**Continuing Party**");

(6) **OSPEDALE SAN RAFFAELE,** as successor in interest to **FONDAZIONE CENTRO SAN RAFFAELE DEL MONTE TABOR**, with registered offices at Via Olgettina 60, 20132 Milan, Italy ("**OSR**" or a "**Continuing Party**"); and

(7) **ORCHARD THERAPEUTICS LIMITED**, a company incorporated under the laws of England and Wales with company number [***] and registered offices at Birchin Court, 20 Birchin Lane, London, EC3V 9DU, England ("**OTL**" or the "**Incoming Party**").

BACKGROUND

(A) This Deed is supplemental to each of the Original Agreements set out in Schedule 1.

(B) The parties hereto have agreed that with effect from the Effective Date that the applicable Outgoing Party or Outgoing Parties shall cease to be party to each Original Agreement and that the Incoming Party shall assume all rights and obligations of the applicable Outgoing Party or Outgoing Parties under each Original Agreement subject to the terms of this agreement and accordingly the applicable Outgoing Party or Outgoing Parties shall be released and discharged from each Original Agreement upon the terms and to the extent set out in this Deed.

AGREED TERMS

1. INTERPRETATION

1.1 The definitions and rules of interpretation in this clause apply to this agreement.

"**APL**"	means the asset purchase and licence agreement relating to rare disease gene therapy assets held by GSK and its affiliates, to be entered into by GGL, GSK IPD, and OTL;
"**Effective Date**"	means the date of execution of the APL;
"**Long Stop Date**"	means [***];
"**Original Agreements**"	means the contracts, amendments, side letters and other ancillary agreements and documents listed in Schedule 1, including the Telethon-OSR Agreement; and
"**Telethon-OSR Agreement**"	means the Research and Development Collaboration and License Agreement dated 15 October 2010 between Telethon, OSR and Glaxo Group Limited relating to a collaboration between the parties for the research, development and commercialisation of certain rare disease gene therapy programmes, as amended from time to time.

1.2 Clause and schedule headings do not affect the interpretation of this Deed.

1.3 A reference to a clause or a schedule is a reference to a clause of, or schedule to, this Deed. A reference to a paragraph is to a paragraph of the relevant schedule, and a reference to an appendix is to the relevant appendix to this Deed.

1.4 A person includes a corporate or unincorporated body.

1.5 Words in the singular include the plural and in the plural include the singular.

1.6 A reference to one gender includes a reference to the other gender.

1.7 A reference to a particular statute, statutory provision or any subordinate legislation made under a statute is to such statute, provision or subordinate legislation as amended or re-enacted from time to time whether before or after the date of this Deed and includes any subordinate legislation made under such statute whether before or after the date of this Deed.

1.8 Where the words include(s), including or in particular are used in this Deed, they are deemed to have the words "without limitation" following them.

1.9 References to this Deed include this Deed as amended or varied in accordance with its terms.

1.10 All capitalised terms not defined herein shall have the meanings given to them in the Telethon-OSR Agreement.

1.11 Notwithstanding the definition of "Effective Date" in the Telethon-OSR Agreement, Effective Date as used in this Deed of Novation shall have the meaning set out in clause 1.1 above.

1.12 The definition of "Major EU Country" and references to the "EU G5 countries" as set forth in the Telethon-OSR Agreement to include the UK shall continue to be interpreted to include the UK by definition, even following the exit of the UK from the European Union.

2. NOVATION

2.1 Substitution of parties

2.1.1 The Incoming Party hereby undertakes to the Continuing Parties to perform each Original Agreement (and the applicable Outgoing Party's or Outgoing Parties' obligations thereunder) and be bound by the terms thereof in every way as if the Incoming Party was, with effect from the Effective Date, a party to the Original Agreement in place of the applicable Outgoing Party or Outgoing Parties.

2.1.2 In consideration of the undertaking in clause 2.1.1 and with the consent of the Continuing Parties and the Incoming Party the applicable Outgoing Party or Outgoing Parties assign all their rights from the Effective Date under each Original Agreement to the Incoming Party.

2.2 Rights and obligations of the parties

2.2.1 Notwithstanding any contrary provision in this Deed the obligation to use Commercially Reasonable Efforts to develop and obtain Regulatory Approval for the ADA-SCID Product in the US (or to use Commercially Reasonable Efforts to launch, promote, manufacture or supply such Product in the US) as set out in section 2.4(b)(ii) of the Telethon-OSR Agreement is irrevocably extinguished on the Effective Date and shall not bind either of GSK or OTL; provided, however that, in the event that the Incoming Party obtains the Regulatory Approval for the ADA-SCID Product in the US and commercialise such Product in the US, the Continuing Parties shall be entitled to be paid by the Incoming Party the applicable milestone payment and royalties in accordance with Section 6.2 and 6.3 of the Telethon-OSR Agreement. This clause 2.2.1 shall be without prejudice to Section 2.4(b)(ii) for any obligations outside of the United States.

2.2.2 Without prejudice to the obligations outside of the United States under Section 2.4(b)(ii), the Incoming Party will use its best efforts to renew the EU Marketing Authorization for the ADA-SCID Product [***] to enable any patients to be treated at OSR from all referring centres globally, as permitted by applicable law.

2.2.3 Clause 3.4 of the Telethon-OSR Agreement shall be deleted from the Telethon-OSR Agreement with effect from the Effective Date.

2.2.4 The Continuning Party and the Incoming Party agree that the obligations of the Outgoing Parties and the Continuing Parties in respect of the research in relation to the Research Program for Vector Manufacturing Improvements and to the Research Program for Lentiviral Platform Improvements envisaged under clause 2.1 and Exhibits E and F of the Telethon-OSR Agreement have been completed and consequently the Incoming Party and the Continuing Parties have no further obligations in relation to such research.

2.2.5 The Incoming Party agrees that the obligations set forth in Section 4.4. of the Telethon-OSR Agreement regarding the Lentiviral Platform Improvements IP and/or the Vector Manufacturing Improvements IP shall only apply with respect to such Improvements arising prior to the date of this Deed of Novation.

2.2.6 Promptly after (and in no event later than [***] from) the Effective Date the Incoming Party shall appoint the Incoming Party's members of the JSC, JPC and JDC, as well as the Alliance Manager.

2.2.7 The Incoming Party shall meet the Continuing Parties within a reasonable period of time (anticipated to be within [***] from the Effective Date) to start good faith discussions with respect to a plan for the development of [***], with the objective to mutually agree in good faith such [***], it being understood that as the exclusive licensee under the Telethon-OSR Agreement, the Incoming Party has sole responsibility to determine and pursue the development and commercialisation of [***], subject always to its diligence obligations under the Telethon-OSR Agreement.

GGL will pay a novation payment to the Continuing Parties equal to a total of [***] on the following condition:

[***] GGL shall pay (or procure the payment of) such amounts within [***] of the receipt of such invoices, to the following account:

OSPEDALE SAN RAFFAELE S.R.L.
[***]

FONDAZIONE TELETHON
[***]

2.2.8 The Continuing Parties and the Incoming Party hereby release and discharge each applicable Outgoing Party, with effect from the Effective Date, from all claims, obligations, demands, duties and liabilities whatsoever in respect of each Original Agreement and the Continuing Parties accept the performance and liability thereof by the Incoming Party in place of performance by and liability of the applicable Outgoing Party for all claims, obligations, demands and duties under each Original Agreement and the Continuing Parties hereby undertake to the Incoming Party, to perform each Original Agreement and be bound by the terms thereof in every way as if the Incoming Party was a party to each Original Agreement in place of the applicable Outgoing Party or Outgoing Parties. For the avoidance of doubt, the Incoming Party shall have no liability under any of the Original Agreements, whether in respect of a breach of the relevant Original Agreement or otherwise, where such liability arose from any event or circumstances occurring prior to the Effective Date, (including, for the avoidance of doubt, the liability under any indemnity included in any of the Original Agreements (including clause 11.1 of the Telethon-OSR Agreement)) or that relates to an Outgoing Party's activities prior to the Effective Date.

2.3 Surviving Obligations

2.3.1 Save as provided in clause 2.2, the Continuing Parties and the Incoming Party shall be liable to the other in respect of their respective obligations and liabilities under each Original Agreement.

3. TERMINATION

3.1 This Deed (and therefore the novation set forth herein) shall become effective among the parties upon the Effective Date; provided, that if the Effective Date has not occurred on or before the Long Stop Date, each party hereto shall be entitled, in its sole discretion and by notice in writing to the other parties, to immediately terminate this Deed.

3.2 In the event of termination under clause 3.1, no party shall have any liability under this Deed and the Outgoing Parties and the Continuing Parties shall remain the sole parties under the Original Agreement and, thus, the Outgoing Parties shall be liable to the Continuing Parties in respect of their respective obligations and liabilities under each Original Agreement, as if this Deed had not been executed.

4. CONFIRMATION OF TERMS

4.1 Save as provided in clause 2.2, the Continuing Parties and the Incoming Party hereby confirm that there have been no unwritten amendments and there are no subsisting waivers in respect of the Original Agreements set out in Schedule 1.

5. LIMITATION PERIODS

5.1 Nothing in this Deed shall have the effect of extending any limitation period set out in, or applicable to, each Original Agreement and nothing in this Deed shall operate to enable any claims to be brought against the Incoming Party whether in tort, contract or otherwise which, but for this Deed, would be statute barred if made against the applicable Outgoing Party or Outgoing Parties.

6. FURTHER ASSURANCES

6.1 Each party to the Deed shall from time to time execute such documents and perform such acts and things as may be required under applicable law to novate each Original Agreement and to give the other parties hereto the full benefit of this Deed.

7. GOVERNING LAW

7.1 This Deed and any dispute arising from the performance or breach hereof any including non-contractual obligations shall be governed by and construed in accordance with the English law.

7.2 No person who is not a party to this Deed shall have any right under the Contracts (Rights of Third Parties) Act 1999 to enforce any term of this Deed.

8. JURISDICTION

8.1 The parties agree that any legal action or proceedings arising out of or in connection with this Deed shall be resolved in accordance with sections 13.1 and 13.2 of the Telethon-OSR Agreement.

[Signatures Follow on Next Page]

IN WITNESS whereof this Deed of Novation has been executed as a deed by the parties hereto on the Effective Date.

EXECUTED and **DELIVERED** as a **DEED** by **GLAXO GROUP LIMITED** acting by a director	)))	
In the presence of:	)	[***] *Director*
Signature of witness:		[***]
Name of witness:		[***]
Address of witness:		[***] [***]
Occupation of witness:		[***]
EXECUTED and **DELIVERED** as a **DEED** by **GLAXOSMITHKLINE RESEACH & DEVELOPMENT LIMITED** acting by a director	)))	
In the presence of:	)	[***] *Director*
Signature of witness:		[***]
Name of witness:		[***]
Address of witness:		[***] [***]
Occupation of witness:		[***]

EXECUTED and **DELIVERED** as a **DEED** by)
GLAXOSMITHKLINE INTELLECTUAL)
PROPERTY DEVELOPMENT LIMITED)
acting by a director

In the presence of:) [***]
)
Director

Signature of witness: [***]

Name of witness: [***]

Address of witness: [***]

[***]

Occupation of witness: [***]

EXECUTED and **DELIVERED** as a **DEED** by)
GLAXOSMITHKLINE S.p.A. in accordance with)
its constitution)
) [***]

EXECUTED and **DELIVERED** as a **DEED** by)
FONDAZIONE TELETHON in accordance with)
its constitution)
) [***]

EXECUTED and **DELIVERED** as a **DEED** by **OSPEDALE SAN RAFFAELE** in accordance with its constitution	)	
	)	[***]
EXECUTED and **DELIVERED** as a **DEED** by **ORCHARD THERAPEUTICS LIMITED** acting by a director	)	
	)	
In the presence of:	)	[***] *Director*
Signature of witness:		[***]
Name of witness:		[***]
Address of witness:		[***]
		[***]
Occupation of witness:		[***]

Schedule 1

THE ORIGINAL AGREEMENTS

Agreement	Date	Parties
Telethon-OSR Agreement, Amendments and Side Letters		
Telethon-HSR Agreement	15 October 2010	GGL, HSR and Telethon
1st Side Letter "MLD clinical trial"	26 June 2012	GGL, HSR and Telethon
Unnumbered Side Letter "Provision of additional services under Research and Development Collaboration and Licence agreement"	2 November 2012	GSK R&D, HSR and Telethon
2nd Side Letter "TIGET-GLP facilities: set-up of additional dedicated rooms"	11 June 2013	GGL, HSR and Telethon
3rd Side Letter "[***]"	28 June 2013	GGL, HSR and Telethon
4th Side Letter	4 September 2013	GGL, HSR and Telethon
5th Side Letter	27 November 2013	GGL, HSR and Telethon
[***]	[***]	[***]
[***]	[***]	[***]
6th Side Letter "MLD clinical trial"	30 August 2014	GSK R&D, OSR and Telethon
7th Side Letter "WAS clinical trial"	30 August 2014	GSK R&D, OSR and Telethon
8th Side Letter "MLD clinical trial"	9 February 2015	GSK R&D, OSR and Telethon
9th Side Letter "WAS clinical trial"	9 February 2015	GSK R&D and Telethon
1st Amendment	31 March 2015	GSK IPDL, OSR and Telethon
10th Side Letter "Agreement for payment of viral vector batch"	11 December 2015	GSK R&D and Telethon
2nd Amendment	4 April 2016	GSK IPDL, OSR and Telethon
3rd Amendment	23 September 2016	GSK IPDL, Telethon and OSR
4th Amendment	15 December 2016	GSK IPDL, OSR and Telethon
[***]	[***]	[***]
5th Amendment	15 July 2017	GGL, OSR and Telethon
6th Amendment	7 November 2017	Telethon, OSR and GSK IPD

Pre-clinical Agreements

[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

Clinical Agreements

[***]	[***]	[***]
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[***]	[***]	[***]
[***]	[***]	[***]

Exhibit 10.5

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "[***]". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT PURSUANT TO RULE 406 PROMULGATED UNDER THE SECURITIES ACT OF 1933, AS AMENDED.

Confidential

DATED October 15th, 2010

Glaxo Group Limited

And

Fondazione Telethon

and

Fondazione Centro San Raffaele del Monte Tabor

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

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This **RESEARCH, DEVELOPMENT, COLLABORATION AND LICENSE AGREEMENT** (the "**Agreement**") is entered into and made effective as of October 15th, 2010 (the "**Effective Date**") by and between (a) Fondazione Telethon, having a registered office at via Carlo Spinola, 16, 00154, Rome, Italy ("**F. Telethon**"), and Fondazione Centro San Raffaele del Monte Tabor, having a registered office at Via Olgettina 60 20132 Milano ("**F. San Raffaele**"), each entity, a not-for-profit corporation incorporated under the laws of Italy, (**F. Telethon** and **F. San Raffaele** are hereinafter referred to jointly as "**TELETHON-HSR**") on the one hand; and, (b) on the other hand, Glaxo Group Limited, a company incorporated under the laws of England and Wales with registered number 00305979, whose registered office is Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex, UB6 0NN, England ("**GSK**"). **TELETHON-HSR** and **GSK** are each referred to herein by name or as a "**Party**" or, collectively, as "**Parties.**"

RECITALS

WHEREAS, in 1995, F. Telethon and F. San Raffaele del Monte Tabor ("F. San Raffaele", and jointly with F. Telethon, the "Foundations") established a collaboration for the creation of the San Raffaele-Telethon Institute for Gene Therapy, an entity without juridical personality (HSR-TIGET), based in Milan, Italy;

WHEREAS, The joint conduct of HSR-TIGET has been disciplined by specific agreements endorsed by both Foundations. The most recent of such agreements, dated July 1st, 2006 was modified by mutual agreement on March 3rd, 2009 is valid until June 30th, 2011 (the "HSR-TIGET Agreement");

WHEREAS, On February 15th, 2010, the Foundations signed an Addendum to the HSR-TIGET Agreement, aimed at disciplining relationships with potential industrial partners for the development of programs of *ex vivo* gene therapy of monogenic hereditary diseases through retroviral and lentiviral platforms, up to the stage of marketing authorization and commercialization of the medicinal products;

WHEREAS, According to such Addendum, F. Telethon is free to negotiate any agreement pursuant to the aims stated above with potential industrial partners, provided that final approval is also obtained by F. San Raffaele;

WHEREAS, F. Telethon and F. San Raffaele will utilize for such a program exclusively the San Raffaele-Telethon Institute for Gene Therapy (HSR-TIGET), therefore, F. Telethon and F. San Raffaele, with respect to any research and clinical activities carried out outside HSR-TIGET which are not carried out by a Third Party acting on behalf of, or as a contractor, service provider or agent of HSR-TIGET are not bound by this Agreement;

WHEREAS, GSK desires to form an alliance with F. Telethon and F. San Raffaele for the research and development and commercialization of programs for *ex vivo* hematopoietic stem cell gene therapy of monogenic hereditary diseases through retroviral and lentiviral platforms, up to the stage of marketing authorization and commercialization of the resulting medicinal products; and

WHEREAS both F. Telethon and F. San Raffaele consider their primary goal that the results of their research become therapeutic solutions to be developed and made available to the benefit of patients.

NOW, THEREFORE, GSK and F. Telethon have agreed to enter into this binding Agreement which sets forth the terms and conditions of an alliance pursuant to this Research and Development Collaboration and License Agreement (the "Agreement"). The Parties to this Agreement are (a) F. Telethon and F. San Raffaele, on the one hand (which are referred to collectively hereinafter as "TELETHON-HSR"), and (b) GSK on the other hand (GSK and F. Telethon and F. San Raffaele are jointly referred to as "Parties" and individually as "Party"). Unless otherwise expressly stated to the contrary in this Agreement, any reference in this Agreement to TELETHON-HSR shall include both F. Telethon and F. San Raffaele. In consideration of the premises and mutual covenants herein contained, which constitute part of this Agreement, the Parties hereto hereby agree as follows:

1 DEFINITIONS

As used in this Agreement, the following terms will have the meanings set forth in this Article 1 unless context dictates otherwise:

"Acceptance" means with respect to a BLA, or NDA, or MAA filed for a Product, (a) in the United States, the receipt by GSK or its Affiliate or Sublicensee of written notice from the FDA in accordance with 21 CFR 314.101(a)(2) that such BLA or NDA is officially "filed", (b) in the European Union, receipt by GSK or its Affiliate or

Sublicensee of written notice of acceptance by the EMEA of such MAA for filing under the centralized European procedure in accordance with any feedback received from European Regulatory Authorities; provided, that if the centralized filing procedure is not used, then Acceptance shall be determined upon the acceptance of such MAA by the applicable Regulatory Authority in the first Major EU Country, (c) in Japan, receipt by GSK or its Affiliate or Sublicensee of written notice of acceptance of filing of such MAA from the MHLW or (d) in any other major market country after receipt by GSK or its Affiliate or Sublicensee of written notice of acceptance of filing of the applicable applications by the competent Regulatory Authority of that specific country.

"ADA-SCID Program Exclusively Licensed IP" means with respect to the ADA-SCID Program: (a) any and all TELETHON-HSR Know-How and Joint Know-How, in each case relating to the ADA-SCID Program or to the composition of matter of, the formulation or delivery of, or the making, use (including method of use) or sale of any Product included within the ADA-SCID Program, or the use of any such Product within the Alliance Scope and (b) any and all TELETHON-HSR Patent Rights and Joint Patent Rights, in each case relating to the ADA-SCID Program or which claims or covers the composition of matter of or the formulation or delivery of, or the making, use (including method of use) or sale of any Product included within the ADA-SCID Program, or the use of any such Product within the Alliance Scope, and (c) or any Vector Manufacturing Improvements IP relating to the ADA-SCID Program.

"Additional Program" means a Collaboration Program within the Alliance Scope that is added under the terms and conditions as set forth in section 6.2 and pertaining to a new disease application, or to a new Vector to be applied to a disease under an existing Collaboration Program under article 2.1.2 (a) through (f) or to be applied to ADA-SCID.

"Adverse Drug Reaction" or "ADR" means any noxious and unintended response to a medicinal product occurring at any dose where there is at least a possibility of a causal link between the administration of the medicinal product and the noxious and unintended response. The foregoing definition is intended to be construed in accordance with International Conference on Harmonisation (ICH) guideline E2A.

"Affiliate" means any Person, which, directly or indirectly through one (1) or more intermediaries, controls, is controlled by or is under common control with a Party to this Agreement, regardless of whether such Affiliate is or becomes an Affiliate on or after the Effective Date. A Person shall be deemed to "control" another Person if it (a) owns, directly or indirectly, beneficially or legally, at least fifty percent (50%) of the outstanding voting securities or capital stock (or such lesser percentage which is the maximum allowed to be owned by a Person in a particular jurisdiction) of such other Person, or has other comparable ownership interest with respect to any Person other than a corporation; or (b) has the power, whether pursuant to contract, ownership of securities or otherwise, to direct the management and policies of the Person. For clarity, F. Telethon and F. San Raffaele are not Affiliates and may not be considered Affiliates hereunder, notwithstanding the relationship between the two Foundations, as indicated in the recitals.

"Alliance Manager" has the meaning assigned to such term in Section 3.3.

"Alliance Scope" means the research, development, manufacture and commercialization of retroviral or lentiviral vectors using *ex vivo* hematopoietic stem cell gene therapy approaches for treating or curing monogenic diseases or disorders.

"Annual Net Sales" means total Net Sales in the Territory in a particular Calendar Year.

"BLA" or "Biologics License Application" means a Biologics License Application (as more fully defined in 21 C.F.R. 600 et seq. or its successor regulations) and all amendments and supplements thereto filed with the FDA.

"Breaching Party" has the meaning assigned to such term in Section 12.2(a).

"Business Day" means a day on which banking institutions in New York, New York, United States, Milan, Italy, and London, England are open for business, excluding any Saturday or Sunday, and excluding the nine (9) consecutive calendar days beginning on December 24th and continuing through January 1st of each Calendar Year during the Term.

"Calendar Day" means any day, including a Saturday, Sunday, Business Day or public or company holiday.

"Calendar Quarter" means a period of three (3) consecutive months ending on the last day of March, June, September, or December, respectively.

"Calendar Year" means a period of twelve (12) consecutive months beginning on January 1 and ending on December 31.

"**cGMP**" means all applicable standards relating to manufacturing practices for fine chemicals, intermediates, bulk products or Products, including (i) the principles detailed in the U.S. Current Good Manufacturing Practices, 21 CFR Parts 210 and 211 and EU Commission Directives 2003/94/EC and 2005/28/EC and The Rules Governing Medicinal Products in the European Community, Volume IV, Good Manufacturing Practice for Medicinal Products, as each may be amended from time to time or (ii) standards promulgated by any governmental body having jurisdiction over the manufacture of a Vector, in the form of laws or regulations.

"Chairperson" has the meaning assigned to such term in Section 3.2(a).

"Claims" has the meaning assigned to such term in Section 11.1.

"Clinical Candidate Selection Criteria" means the criteria (a) set forth in Exhibit A, and (b) as modified by the JSC for Vectors in each Collaboration Program pursuant to Section 2.5(a), for achievement of the Clinical Candidate Selection Milestone.

"Collaboration Program" means the program of Research and Development activities to be conducted by TELETHON-HSR and GSK under the alliance pursuant to this Agreement for each of the following Programs:

a. Wiskott-Aldrich Syndrome

b. Chronic granulomatous Disease

c. Metachromatic leukodystrophy

d. Globoid cell leukodystrophy

e. Mucopolysaccaridosis Type I (Hurler)

f. Beta-thalassemia

g. "**Additional Programs**" will be added upon the terms and conditions set forth in section 6.2 and will be identified during the Research Term.

"Collaboration Program Exclusively Licensed IP" means with respect to the relevant Collaboration Program: (a) any and all TELETHON-HSR Know-How and Joint Know-How, in each case relating to the relevant Collaboration Program or to the composition of matter of, the formulation or delivery of, or the making, use (including method of use) or sale of any Product included within the Collaboration Program, or the use of any such Product within the Alliance Scope and (b) any and all TELETHON-HSR Patent Rights and Joint Patent Rights, in each case relating to the relevant Collaboration Program or which claims or covers the composition of matter of or the formulation or delivery of, or the making, use (including method of use) or sale of any Product included within the Collaboration Program, or the use of any such Product within the Alliance Scope, and (c) any Lentiviral Platform Improvements IP relating to the Collaboration Program or Vector Manufacturing Improvements IP relating to the Collaboration Program. For the avoidance of doubt, GSK shall not have an exclusive license to the Collaboration Program Exclusively Licensed IP unless and until such time as GSK exercises its Option with respect to the relevant Collaboration Program or by operation of the applicable termination provisions of Article 12.

"**Commercially Reasonable Efforts**" means the following: (a) with respect to TELETHON-HSR, such efforts that are consistent with the efforts and resources normally used by TELETHON-HSR in the exercise of its reasonable business discretion relating to the research, development and commercial progression of a potential biopharmaceutical product owned by it or to which it has exclusive rights, with similar product characteristics as the relevant Vector or Product, which is of similar market potential at a similar stage in its development or product life as the relevant Vector or Product, taking into account issues of scientific risk, patent coverage, safety and efficacy, product profile, competitiveness of the marketplace, proprietary position, the regulatory structure involved and profitability (including pricing and reimbursement status achieved or likely to be achieved) and other relevant factors, including without limitation, technical, legal, scientific and/or medical factors; and (b) with respect to GSK, such efforts that are consistent with the efforts and resources

normally used by GSK in the exercise of its reasonable business discretion relating to the development and commercialization of a prescription biopharmaceutical product owned by it or to which it has exclusive rights, with similar product characteristics as the relevant Vector or Product, which is of similar market potential at a similar stage in its development or product life as the relevant Vector or Product, taking into account issues of scientific risk, patent coverage, safety and efficacy, product profile, the competitiveness of the marketplace, the proprietary position, the regulatory structure involved and profitability (including pricing and reimbursement status achieved or likely to be achieved) and other relevant factors, including without limitation, technical, legal, scientific and/or medical factors provided that GSK shall not be entitled to factor in amounts that would be owed to TELETHON-HSR relating to the relevant Product.

"Competitive Infringement" has the meaning assigned to such term in Section 8.5(a).

"Confidential Information" has the meaning assigned to such term in Section 9.1.

"Control," "Controls," "Controlled" or "Controlling" means, with respect to any intellectual property, possession of the ability to grant the licenses or sublicenses as provided herein without violating the terms of any agreement or other arrangement with any Third Party. A Party shall be deemed to Control Joint IP to the extent of its individual or joint interest therein, as applicable.

"Develop" or **"Development"** means pre-clinical and clinical drug development activities relating to the development of Vectors, Products and/or processes and submission of information to a Regulatory Authority for the purpose of obtaining Regulatory Approval and Reimbursement Approval of a Product, and activities to develop manufacturing capabilities for Products. Development includes, but is not limited to, pre-clinical activities, toxicology studies, formulation, manufacturing process development and scale-up (including bulk Vector production), manufacturing Vector or Product for Clinical Trials, quality assurance and quality control, technical support, pharmacokinetic studies, clinical studies and regulatory affairs activities.

"Development Plan" has the meaning assigned to such term in Section 2.2(c).

"Disclosing Party" has the meaning assigned to such term in Section 9.1.

“EMA” means the European Medicines Agency, and any successor entity thereto.

“European Commission” means the executive body of the European Union that has legal authority to grant marketing authorization approvals for pharmaceutical products in the European Union following scientific evaluation and recommendation from the EMA or other applicable Regulatory Authorities.

“European Union” or **“EU”** means all countries that are officially recognized as member states of the European Union at any particular time during the Term.

“Executive Officers” means the executive officers designated by each Party as having the final decision-making authority with respect to the particular dispute being presented for resolution pursuant to Sections 3.1, 3.2 and 5.1.

“Exclusively Licensed IP” means, collectively, the Collaboration Program Exclusively Licensed IP and the ADA-SCID Program Exclusively Licensed IP.

“FDA” means the U.S. Food and Drug Administration, and any successor entity thereto.

“Field” means gene therapy of any monogenic disorder, disease or condition.

“First Commercial Sale” means, with respect to each Product, the first sale for which revenue has been recognized by GSK or TELETHON-HSR or their respective Affiliate or Sublicensees for use or consumption by the general public of such Product in any country in the Territory after all required Regulatory Approvals and Reimbursement Approvals have been granted, or such sale is otherwise permitted, by the Regulatory Authority in such country (e.g. [***]), provided, that, the following shall not constitute a First Commercial Sale: (a) any sale to an Affiliate or Sublicensee unless the Affiliate or Sublicensee is the last entity in the distribution chain of the Product and (b) any use of such Product in Clinical Trials, preclinical activities or other Research or Development activities, or disposal or transfer of Products for a bona fide charitable purpose.

“Generic Competition” means with respect to the GSK Product(s) in any particular country, the existence of any Generic Product(s) in direct competition with such GSK Product(s) in such country that amount to more than [***] of the market for such GSK Product(s) in such country.

“Generic Product” means any biopharmaceutical or biosimilar product that (a) is sold by a Third Party that is not a licensee or Sublicensee of GSK or its Affiliates, or any of their licensees or Sublicensees, under a marketing authorization granted by a Regulatory Authority to such Third Party and (b) contains the same or a similar Vector as an active pharmaceutical ingredient as the relevant Product and (c) (i) for purposes of the United States, is approved in reliance, in whole or in part, on the prior approval of a Product or on the safety and efficacy data generated for the prior approval of a Product, in each case as determined by the FDA, or (ii) for purposes of a country outside the United States, is approved in reliance, in whole or in part, on the prior approval of a Product or on the safety and efficacy data generated for the prior approval of a Product, in each case as determined by the applicable Regulatory Authority.

“**GSK Development Vector**” means any Vector, arising out of (i) the exclusively licensed ADA-SCID Program, pursuant to Section 4 or (ii) a Collaboration Program that has become a GSK Development Program upon GSK’s exercise of the applicable Option.

“GSK Development Plan” shall have the meaning assigned to it in Section 5.1(d).

“**GSK Development Program**” means each of (i) the ADA-SCID Program, and (ii) any Collaboration Program for which GSK has exercised its Option and, for both (i) and (ii), where such Program has not been terminated by GSK or terminated by TELETHON-HSR (i.e for a termination by TELETHON-HSR in the case of an uncured material breach by GSK of its diligence or other obligations with respect to such Program).

“GSK IP” means GSK Know-How and GSK Patent Rights.

“GSK Know-How” means Know-How that is solely owned or otherwise Controlled by GSK and is (i) discovered, developed, invented or created solely by or on behalf of GSK as of the Effective Date or at any time during the Term of this Agreement pursuant to, and is utilized and incorporated in, a Collaboration Program or a GSK Development Program and (ii) necessary or useful for the Research, Development making, use or sale of Vectors.

“GSK Patent Rights” means all Patent Rights solely owned or otherwise Controlled by GSK as of the Effective Date or at any time during the Term of the Agreement which claim or cover GSK Know-How.

“GSK Product” means a Product Developed and commercialized by GSK or its Affiliate or Sublicensee under or resulting from a GSK Development Program.

“Indemnitee” has the meaning assigned to such term in Section 11.3.

“Joint IP” means Joint Know-How and Joint Patent Rights.

“Joint Know-How” means, at any time during the Term of this Agreement, Know-How that is discovered, developed, invented or created jointly by or on behalf of employees, agents and/or consultants and/or contractors and/or collaborators of (1) TELETHON -HSR working within, or working on behalf of, HSR-TIGET and/or its Affiliate on the one hand, and on the other hand, by or on behalf of employees, agents and/or consultants and/or contractors of (2) GSK and/or its Affiliate, or any Third Party collaborator of TELETHON-HSR where relevant and permissible under a Third Party agreement existing on the Effective Date or entered into during the Term of this Agreement.

“Joint Patent Rights” means, at any time during the Term of this Agreement, Patent Rights owned jointly by (1) TELETHON-HSR and/or its Affiliate on the one hand, and (2) on the other hand, by GSK and/or its Affiliate, or by any Third Party collaborator of TELETHON-HSR where relevant and permissible under a Third Party agreement existing on the Effective Date or entered into during the Term of this Agreement, covering or claiming Joint Know-How.

“Joint Patent Subcommittee” or **“JPS”** has the meaning assigned to such term in Section 3.2(g).

“Joint Steering Committee” or **“JSC”** has the meaning assigned to such term in Section 3.2.

“Know-How” means all (a) information, techniques, technology, practices, trade secrets, inventions (whether patentable or not), methods, knowledge, know-how, skill, experience, data, results (including pharmacological, toxicological and clinical

test data and results, and Research or Development data, reports and batch records), clinical, safety, analytical and quality control data, analytical methods (including applicable reference standards), full batch documentation, packaging records, release, stability, storage and shelf-life data, manufacturing process information and quality control data, results or descriptions, software and algorithms, regulatory filings, pharmaceutical data, instructions, processes, procedures, formulas, drawings, technical and non-technical data and (b) compositions of matter, cells, cell lines, assays, animal models and physical, biological or chemical material. As used in this definition, "**clinical test data**" shall be deemed to include all information related to the clinical or pre-clinical testing of a Vector or Product, including without limitation patient report forms, investigators' reports, biostatistical, pharmaco-economic and other related analyses, regulatory filings and communications, and the like.

"Lead Vector" means a Vector which is the most advanced Vector within the Program.

"Lentiviral Platform Improvements IP" means, collectively, any and all TELETHON-HSR Know-How and Joint Know-How and TELETHON-HSR Patents and Joint Patents existing or arising under the Research Program for Lentiviral Platform Improvements or under any Program hereunder or which is otherwise generated by or on behalf of TELETHON-HSR, or in collaboration with a Third Party where relevant and permissible under a Third Party agreement existing on the Effective Date or entered into during the Term of this Agreement, during the Term relating to the technology platform for the use of lentiviral vectors for *ex vivo* hematopoietic stem cell gene therapy of monogenic diseases, disorders or conditions.

"Losses" has the meaning assigned to such term in Section 11.1.

"MAA" means a regulatory application filed with the EMA or MHLW seeking Regulatory Approval of a Product, and all amendments and supplements thereto filed with the EMA or MHLW.

"Major EU Country" means any of the United Kingdom, Germany, France, Spain or Italy.

"Market Exclusivity Rights" means (a) a marketing exclusivity right conferred upon the sponsor of a drug for a rare disease or condition under 21 United States Code

Section 360cc, any analogous provision of law applicable in any other country in the Territory, or any provision of law that is a successor to them; and (b) "market exclusivity" that is additive or complementary to that specified in the preceding clause "a" that is earned and granted as a result of the conduct of specified paediatric studies, under 21 United States Code Section 355a, any analogous provision of law applicable in any other country in the Territory, or any provision of law that is a successor to them.

"Materials" has the meaning assigned to such term in Section 2.8.

"MHLW" means the Ministry of Health, Labour and Welfare of Japan, or the Pharmaceuticals and Medical Devices Agency (the "PMDA," formerly known as IYAKUHIN SOGO KIKO), or any successor to either of them, as the case may be.

"Milestone Criteria" means either Clinical Candidate Selection Criteria, Six Month Safety and Data Review During PhI/II Extension Study Criteria or Proof of Concept Criteria, as the case may be.

"Milestone Report" has the meaning assigned to such term in Section 2.6(a).

"NDA" means a New Drug Application (as more fully defined in 21 C.F.R. 314.5 *et seq.* or its successor regulation) and all amendments and supplements thereto filed with the FDA.

"Net Sales" means, with respect to any Product, the gross invoiced sales price of such Product sold by GSK or their respective Affiliates or Sublicensees (the "**Selling Party**"), but excluding [***] as reported by the Selling Party in its financial statements in accordance with the International Financial Reporting Standards ("IFRS") for GSK or TELETHON-HSR (or any other Selling Party which accounts in accordance with IFRS) applied on a consistent basis, for:

(a) [***];

(b) [***];

(c) [***];

(d) [***];

(e) [***]; and

(f) [***].

Sales between GSK and its Affiliates or Sublicensees, or TELETHON-HSR and its Affiliates or Sublicensees, as applicable, shall be excluded from the computation of Net Sales, and no payments will be payable on such sales except where such Affiliate or Sublicensee is the end user in the distribution chain for the Product, in which case such sales shall be deemed to be at a price which is equivalent to the price which would normally be charged on an arms' length basis for equivalent sales.

For purposes of determining royalties and sales milestones payable on Combination Products, Net Sales will be calculated as follows, in each [***]:

If a Product is sold as part of a Combination Product (as defined below), Net Sales will be the product of (i) Net Sales of the Combination Product calculated as above (i.e., calculated as for a non-Combination Product) and (ii) the fraction (A/(A+B)), where:

A is [***]

B is [***].

If A or B cannot be determined by reference to non-Combination Product sales as described above, then Net Sales for purposes of determining royalty payments will be calculated as above, but the average wholesale acquisition cost in the above equation shall be determined by mutual agreement reached in good faith by the Parties prior to the end of the accounting period in question based on an equitable method of determining same that takes into account, in the applicable country, variations in dosage units and the relative fair market value of each therapeutically active ingredient in the Combination Product. If the Parties are unable to reach such an agreement prior to the end of the applicable accounting period, then the Parties will refer such matter to a jointly selected Third Party with expertise in the pricing of pharmaceutical products that is not an employee, consultant, legal advisor, officer, director or stockholder of, and does not have any conflict of interest with respect to, either Party for resolution in accordance with Section 13.1(b). As used in this Agreement, "Combination Product" means a Product that contains one or more

additional active ingredients (whether co-formulated or co-packaged) that are neither Vectors nor generic or other non-proprietary compositions-of-matter. Pharmaceutical dosage form vehicles, adjuvants and excipients shall be deemed not to be "active ingredients"

"Non-breaching Party" has the meaning assigned to such term in Section 12.2(a).

"Option" has the meaning assigned to such term in Section 4.2(a).

"Option Exercise Fee" means the fee payable by GSK on exercise of an Option as set out in Section 6.2.

"Option Period Start" has the meaning assigned to such term in Section 4.2(d) (i).

"Option Point" means the date upon which GSK exercises its Option.

"Party" or "Parties" has the meaning assigned to such term in the Preamble.

"Patent Costs" means the reasonable fees and expenses paid to outside legal counsel, and filing, maintenance and other out-of-pocket expenses paid to Third Parties, incurred in connection with the Prosecution and Maintenance of Patents.

"Patent/Market Exclusivity Royalty" has the meaning assigned to such term in Section 6.3(a).

"Patent Rights" means (a) all patents and patent applications in any country or supranational jurisdiction in the Territory, (b) any substitutions, divisions, continuations, continuations-in-part, provisional applications, reissues, renewals, registrations, confirmations, re-examinations, utility models, inventors certificates, patent term extensions including supplementary protection certificates, paediatric patent term extensions and the like of any such patents or patent applications, and (c) foreign counterparts of any of the foregoing.

"Payee" has the meaning assigned to such term in Section 6.7.

"Payor" has the meaning assigned to such term in Section 6.7.

"Person" means any individual, partnership, joint venture, limited liability company, limited liability partnership, corporation, firm, trust, association, unincorporated organization, governmental authority or agency, or any other entity not specifically listed herein.

“Product” means any product that includes a Vector designed or intended for gene therapy within the Field, including, for example, a patient’s cell transduced with the Vector, whether or not as the sole active ingredient, and in any dosage form or formulation.

“Program” means the ADA-SCID Program, a Collaboration Program, a TELETHON-HSR Development Program, or a GSK Development Program, as applicable.

“Proof of Concept” or **“POC”** means the stage of Development at which a Lead Vector has successfully satisfied the Proof of Concept Criteria.

“Proof of Concept Criteria” or **“POC Criteria”** means the clinical and the non-clinical criteria established by the JSC, pursuant to Section 2.5 (b), which is designed to determine whether a Lead Vector demonstrates Proof of Concept, that is, (i) the endpoints and parameters for the Proof of Concept Study designed to indicate a degree of efficacy, for example determined by the level of gene expression, required to signal differentiation in a particular indication in patients with the disease under study with the appropriate safety profile for such indication, and (ii) the associated non-clinical Proof of Concept Criteria, that is, the non-clinical safety assessment, metabolism, pharmacokinetics and chemical manufacture and control criteria to be defined by the JSC on a Collaboration Program-by-Collaboration Program basis.

“Proof of Concept Study or **“POC Study”** shall mean, with respect to a particular Lead Vector, the first human Clinical Trial of such Lead Vector, carried out in accordance with normal industry standards, that meets the requirements of 21 C.F.R. Section 312.21(b), unless otherwise agreed by the JSC, and is intended to explore the effectiveness and signal for differentiation of the Lead Vector for a particular indication in patients with the disease under study and to determine the common short-term side effects and risks associated with the drug and thus to satisfy the clinical Proof of Concept Criteria if successful. For clarity, the Proof of Concept Study is intended only to provide evidence of efficacy as described above of a particular Lead Vector and is not intended to be a pivotal trial or dose-ranging study or otherwise to provide data sufficient to support any Regulatory Approval.

“Proof of Concept Study Design” or **“POC Study Design”** means the design, content and endpoints for a Proof of Concept Study.

“Prosecution and Maintenance” or **“Prosecute and Maintain”** means, with regard to a Patent Right, the preparing, filing, prosecuting and maintenance of such Patent Right, as well as re-examinations, reissues, and requests for patent term adjustments, patent term extensions and supplementary protection certificates with respect to such Patent, together with the initiation or defense of interferences, the initiation or defense of oppositions, revocation and invalidity proceedings, and other similar proceedings with respect to the particular Patent, and any appeals therefrom. For clarification, “Prosecution and Maintenance” or “Prosecute and Maintain” shall not include any other enforcement actions taken with respect to a Patent.

“Receiving Party” has the meaning assigned to such term in Section 9.1.

“Regulatory Approval” means any and all approvals, licenses, registrations, or authorizations of any country, federal, supranational, state or local regulatory agency, department, bureau or other government entity that are necessary for the manufacture, use, storage, import, transport and/or sale of a particular Product in the applicable jurisdiction.

“Regulatory Authority” means the FDA in the U.S. or any health regulatory authority in another country in the Territory that is a counterpart to the FDA and holds responsibility for granting regulatory marketing approval for a Product in such country, including the European Commission and the MHLW, and any successor(s) thereto.

“Reimbursement Approval” means any and all pricing and/or reimbursement approvals, licenses, registrations, or authorizations of any country, federal, supranational, state or local regulatory agency, department, bureau or other government entity, or by a payor or charitable organisation relating to the sale or transfer of a particular Product in the applicable jurisdiction including in the EU applicable reimbursement in a Major EU Country, in the U.S. applicable first reimbursement by the first applicable agency, payor or organisation, in Japan applicable first reimbursement by the first applicable agency, payor or organisation, and in any other jurisdiction applicable first reimbursement by the first applicable agency, payor or organisation in such jurisdiction.

“Research” means the discovery, identification, research, characterization, modification, derivatization, improvement, optimization, and pre-clinical testing of ex vivo stem cell gene therapy Vectors.

“Research Term” has the meaning assigned to such term in Section 2.3.

“Review Period” has the meaning assigned to such term in Section 4.2(d).

“Research Program for Lentiviral Platform Improvements” means the activities of TELETHON-HSR, as outlined generally in Exhibit E, to be conducted during the Term, in collaboration with GSK and/or its Affiliates under this alliance, or independently by or on behalf of TELETHON-HSR, or, where relevant and permissible under a Third Party agreement, in collaboration with a Third Party, to research and develop the technology platform for the use of lentiviral vectors for ex vivo hematopoietic stem cell gene therapy for treating or curing monogenic disorders, diseases or conditions.

“Research Program for Vector Manufacturing Improvements” means the activities of GSK and/or its Affiliates, as outlined generally in Exhibit F, to be conducted during the Term in collaboration with TELETHON-HSR and/or its Affiliates under this alliance, or independently by or on behalf of GSK, or, where relevant and permissible under a Third Party agreement, in collaboration with a Third Party, to research and develop improvements relating to the manufacture of retroviral or lentiviral vectors for ex vivo hematopoietic stem cell gene therapy.

“Serious Adverse Event” or “SAE” means any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

“Subcommittee” has the meaning assigned to such term in Section 3.2(f).

“Sublicensee” means, with respect to a particular Product, an Affiliate or a Third Party to whom GSK or TELETHON-HSR, as applicable, has granted a sublicense or license under any TELETHON-HSR IP and/or Joint IP and/or GSK IP licensed to such Party, as permitted in accordance with the provisions of this Agreement, but excluding any Third Party acting solely as a distributor.

“TELETHON-HSR Development Program” means a Collaboration Program for which GSK fails to exercise its Option before expiration or GSK declines its Option, a Collaboration Program that is terminated by the JSC or GSK, or a terminated GSK Development Program, where such Program has been terminated by GSK or TELETHON-HSR by operation of the applicable provisions of Article 12 containing Vectors and Products that TELETHON-HSR elects to further Develop and commercialize.

“TELETHON-HSR IP” means the TELETHON-HSR Know-How and the TELETHON-HSR Patent Rights.

“TELETHON-HSR Know-How” means Know-How that is (i) solely owned or otherwise Controlled by TELETHON-HSR and/or is discovered, developed, invented or created solely by or on behalf of employees, agents, consultants, contractors and/or collaborators working within HSR-TIGET or on behalf of TELETHON-HSR, that is existing as of the Effective Date or generated at any time during the Term of this Agreement pursuant to a Program and (ii) necessary or useful to the Program or the Research, Development making, use or sale of Vectors or Products.

“TELETHON-HSR Patent Rights” means all Patent Rights solely owned or otherwise Controlled by TELETHON-HSR as of the Effective Date or at any time during the Term of this Agreement which cover or claim TELETHON-HSR Know-How, including, without limitation, those listed on Exhibit D, which is to be updated as necessary from time to time.

“TELETHON-HSR Product” means a Product Developed and commercialized by TELETHON-HSR under a TELETHON-HSR Development Program.

“Term” has the meaning assigned to such term in Section 12.1.

“Territory” means the entire world.

“Third Party” means any Person other than TELETHON-HSR or GSK or an Affiliate of TELETHON-HSR or GSK.

“United States” or “U.S.” means the United States of America and all of its territories and possessions.

"VAT" means the tax imposed by Council Directive 2006/112/EC of the European Community and any national legislation implementing that directive together with legislation supplemental thereto and in particular, in relation to the United Kingdom, the tax imposed by the Value Added Tax Act.

"Valid Claim" means any claim within a pending, allowed or issued U.S. patent application or patent, or pending, issued patent application or patent in a jurisdiction outside the U.S., that: (a) has not expired, lapsed, been cancelled or abandoned, or been dedicated to the public, disclaimed, or held unenforceable, invalid, revoked or cancelled by a court or administrative agency of competent jurisdiction in an order or decision from which no appeal has been or can be taken, including without limitation through opposition, re-examination, reissue or disclaimer and (b) in the case of a pending patent application, has not been pending for more than [***] from the earliest priority date claimed in the relevant country, provided that such patent application was prosecuted in good faith by TELETHON-HSR.

"Vector" means any retroviral or lentiviral gene therapy vector, for the relevant Program, together with its gene insert, (a) that is existing as of the Effective Date in relation to the Program or (b) that arises under a Collaboration Program, or (c) that is identified, modified, derivatized, improved, optimized or otherwise Researched or Developed by TELETHON-HSR or its Affiliate or by GSK under a Collaboration Program or a GSK Development Program.

"Vector Manufacturing Improvements IP" means, collectively, any and all GSK or TELETHON-HSR Know-How and Joint Know-How and GSK or TELETHON-HSR Patents and Joint Patents existing or arising under the Research Program for Vector Manufacturing Improvements or under any Program hereunder or which is otherwise generated by or on behalf of TELETHON-HSR or in collaboration with a Third Party where relevant and permissible under a Third Party agreement existing on the Effective Date or entered into during the Term of this Agreement, during the Term relating to the manufacture of retroviral or lentiviral vectors for *ex vivo* hematopoietic stem cell gene therapy of monogenic diseases, disorders or conditions.

2 RESEARCH AND DEVELOPMENT UNDER THE ALLIANCE

2.1 Overview

The intent and objective of the alliance under this Agreement is to 1) develop and commercialize an *ex vivo* hematopoietic stem cell gene therapy franchise comprised of several different product candidates for treating or curing multiple monogenic disorders and 2) to further optimize lentivirus vectors for *ex vivo* gene therapy of monogenic diseases, disorders or conditions. The "Alliance Scope" is defined as the research, development, manufacture and commercialization of retroviral or lentiviral vectors using *ex vivo* hematopoietic stem cell gene therapy approaches for treating or curing monogenic diseases, disorders or conditions. The alliance hereunder will include the ADA-SCID Program, the Collaboration Programs (including any Additional Programs that are selected by GSK), the Research Program for Lentiviral Platform Improvements and the Research Program for Vector Manufacturing Improvements. An overview of the alliance hereunder is described below:

1. Retrovirus-based GSK Development Program
    a. ADA-SCID Program
2. Lentivirus-based Collaboration Programs
    a. Wiskott-Aldrich Syndrome
    b. Chronic granulomatous Disease
    c. Metachromatic leukodystrophy
    d. Globoid cell leukodystrophy
    e. Mucopolysaccaridosis Type I (Hurler)
    f. Beta-thalassemia
    g. Additional Programs related to monogenic diseases, disorders or conditions to be added upon the terms and conditions set forth in section 6.2 and to be identified during the Research Term.
3. Research Programs, for
    a. Lentiviral Platform Improvements necessary or useful for the Collaboration Programs

b. Vector Manufacturing Improvements necessary or useful for the Collaboration Programs

The Research Program for Lentiviral Platform Improvements and the Research Program for Vector Manufacturing Improvements will involve collaboration between the Parties as well as independent activities by TELETHON-HSR or GSK, and activities by TELETHON-HSR with a Third Party where relevant and permissible under Third Party agreements existing on the Effective Date or entered into during the Term of this Agreement, with respect to researching and developing improvements to the relevant *ex-vivo* gene therapy platform, which includes, for example, improvements to the retroviral and lentiviral vector platform, the cell transduction methodology, and the bone marrow transplantation methodology, and vector production and optimization.

Research Program for Vector Manufacturing Improvements

This Research Program will be as outlined generally in Exhibit F and will include, but not be limited to, activities such as further improvements and scale up of transient transfection and downstream process and stable packaging cell line generation. Such activities are envisaged as GSK independent activities or as jointly undertaken activities through cooperation between the Parties. Jointly undertaken activities between the Parties will be overseen by the JSC, with GSK taking on most of the wet activities and costs. TELETHON-HSR will provide to GSK and its Affiliates expert advice and reagents at no cost to GSK. Each Party will incur and be responsible for its own costs.

Research Program for Lentiviral Platform Improvements

This Research Program will be as outlined generally in Exhibit E and will include, but not be limited to, activities performed by TELETHON-HSR independently of GSK, or in collaboration with GSK hereunder, or, where relevant and permissible under Third Party agreements, by TELETHON-HSR in collaboration with a Third Party under existing or arising agreements with such Third Party during the Term. Jointly undertaken activities between the Parties, except for Third Party collaborations, will be overseen by the JSC, with TELETHON-HSR and its Third

Party collaborators taking on most of the wet activities and costs. TELETHON-HSR shall provide to GSK and its Affiliates privileged access to use the licenses described in Article 4 and to use the results of this research so that arising data and improvements can be incorporated under any Program during the Term as is useful or necessary. Each Party will incur and be responsible for its own costs.

2.2 Obligations of the Parties in General

The general obligations of each Party for the ADA-SCID Program and the Collaboration Programs shall be as follows:

(a) TELETHON-HSR at its own cost, shall be responsible as follows:

i. To progress all Collaboration Programs through clinical Development to the completion of clinical Proof of Concept studies *(see Exhibit C for general proof of concept "PoC" criteria)*. It is anticipated, and both Parties agree, that GSK will provide regulatory guidance to support TELETHON-HSR activities.

ii. To produce research and early clinical grade material as needed for all Collaboration Programs up to the Option Point, unless GSK elects, in its sole discretion, to conduct such activities or to use a Third Party manufacturer of GSK's choice to conduct such activities, at GSK's own cost, subject to the prior approval of the JSC, such approval not to be withheld by TELETHON-HSR unless for compelling reasons relating to Vector or Product quality, scientific considerations, or material delay to critical Program timelines, that in each case, cannot reasonably be overcome. GSK's costs in the event of such election by GSK to conduct such activities or use a Third Party manufacturer shall include any non-cancellable and committed costs owed by TELETHON-HSR to a Third Party manufacturer under contractual obligations which cannot be mitigated or avoided by TELETHON-HSR's reasonable efforts.

iii. TELETHON-HSR will not have obligations or responsibilities for conducting any of the commercial activities of the ADA-SCID Program or for any Collaboration Program either before or after the Option Point.

(b) GSK, at its own cost, and having final decision-making authority, as of the Option Point for each Collaboration Program (or as of the Agreement Effective Date for the ADA-SCID Program), shall be responsible as follows:

i. To produce clinical and commercial supplies of material as needed on a global basis, unless GSK elects to use a Third Party manufacturer, to be selected by GSK at its sole discretion.

ii. To conduct and manage all regulatory activities either alone or, if GSK elects to do so, via TELETHON-HSR, but with GSK having final say, on all such matters, even those carried out via TELETHON-HSR, subject to GSK reimbursing TELETHON-HSR's reasonable and documented costs for conducting such activities, if requested by GSK. It is anticipated, and if agreed in writing in advance by GSK at the JSC, that TELETHON-HSR may remain responsible for and sponsor an ongoing clinical study that was initiated by TELETHON-HSR prior to the Option Point, provided, however, that GSK shall reimburse TELETHON-HSR its reasonable and documented costs for conducting such activities after the exercise of the Option, if requested by GSK, and GSK shall have the final say on all aspects of the conduct and progression of the Program after exercise by GSK of the Option right, provided that GSK must act reasonably in any such request for TELETHON-HSR to conduct such activities, and will not require Telethon-HSR to do anything that would be unethical, breach any applicable law or be in breach of the relevant ethically approved protocol.

iii. To conduct all commercial activities on a global basis and, save the occurrence of extraordinary force majeure events (as defined in Section 13.6), to use its Commercially Reasonable Efforts to commercialize the ADA-SCID Program and the Programs for which it exercises its Option throughout the Territory upon the exercise of the Option Right in accordance with the terms of Section 5.1(c).

(c) Each Collaboration Program will be carried out by TELETHON-HSR pursuant to a development plan (each, a "Development Plan") that will outline anticipated Research and Development activities to be conducted by TELETHON-HSR, the anticipated timelines for carrying out such activities and the criteria to be met in reaching the Program milestones to enable a determination on completion of

the relevant activities as to whether all of the applicable Milestone Criteria have been met. Any estimates regarding the timelines of such activities shall be intended as a general guide only. Development Plans for the Programs will be prepared by TELETHON-HSR following the Effective Date and submitted to the JSC for comment and approval. TELETHON-HSR shall consider all comments of the JSC in good faith and shall prepare a final Development Plan for approval by the JSC promptly following receipt of such comments.

(d) From time to time during the Research Term, TELETHON-HSR shall update each Development Plan (or applicable portion thereof) and shall submit such updated Development Plan to the JSC for review and comment. TELETHON-HSR shall consider all such comments in good faith before preparing an updated Development Plan. Each updated Development Plan shall replace the Development Plan previously in effect. Each Development Plan will be reviewed as necessary at each meeting of the JSC, and at any other time upon the request of either Party, and the JSC may suggest modifications, as appropriate, to reflect material scientific or commercial developments. In the event of any inconsistency between any Development Plan and this Agreement, the terms of this Agreement shall prevail and any such inconsistent portion of a Development Plan shall be amended on a timely basis.

(e) Each Party contemplates the possibility of hosting visiting scientists from the other Party for activities related to the Alliance Scope. In such case, the Parties will apply appropriate and mutually-acceptable visiting scientist agreements.

2.3 **Research Term**

The Research term shall commence on the Effective Date and shall expire, on a Program-by-Program basis, upon the earlier of (i) five (5) years after the Effective Date, or (ii) the date that the last Option with respect to any Collaboration Program is exercised or expires un-exercised by GSK (unless terminated earlier in accordance with this Agreement) (the "**Research Term**"), subject to extension if mutually agreed in writing by the Parties.

2.4 **The ADA-SCID Program and the Collaboration Programs**

(a) TELETHON-HSR Rights and Responsibilities.

(i) *The Collaboration Programs*. Prior to GSK's exercise of an Option with respect to a Collaboration Program, TELETHON-HSR shall have responsibility for the conduct of the Research and Development of each Vector (including, but not limited to, Clinical Trials and submissions to Regulatory Authorities) under such Collaboration Program in accordance with the applicable Development Plan. TELETHON-HSR shall be solely responsible for all internal and external costs and expenses in connection with the Collaboration Programs up to the date of GSK's exercise of an Option in relation to such a Collaboration Program. *TELETHON-HSR Development Activities after Option Exercise:* After the Option Exercise Date for a given Collaboration Program, and only if and to the extent mutually agreed in writing by the Parties, TELETHON-HSR will have the limited right to conduct those specific Development activities as may be mutually agreed in writing by the Parties, and all such activities shall be subject to the sole decision-making authority of GSK. Subject to a budget agreed upon in advance by the Parties, GSK shall bear the costs and expenses associated with all such Development activities, which may also include pre-clinical and CMC (Chemistry Manufacturing & Control) activities, conducted by TELETHON-HSR pursuant to this Section 2.4, and TELETHON-HSR will invoice GSK for such costs and expenses on a [***] basis. TELETHON-HSR's obligation to conduct each Collaboration Program shall terminate at the earlier of (i) GSK's exercise of the Option with respect to such Collaboration Program, (ii) expiration of the Research Term, as may be extended pursuant to Section 2.3, or (iii) a decision being made by the JSC to terminate such Collaboration Program.

(b) Diligence.

(i) Collaboration Programs. The objective of each Collaboration Program is to (i) discover and Develop a Lead Vector for each Program for further Development under the terms of this Agreement and (ii) progress each Lead Vector to the completion of the POC Study. The JSC will commence a review at the point at which the

first Lead Vector(s) is within [***] of achieving the Clinical Candidate Selection Criteria (or as otherwise may be earlier agreed by the JSC) in the relevant Collaboration Program to determine the liabilities associated with such Lead Vector(s). During the Research Term, TELETHON-HSR shall use Commercially Reasonable Efforts to conduct each Collaboration Program and related Research and Development activities for such Collaboration Program in accordance with the applicable Development Plan once such plan has been approved by the JSC in accordance with Section 2.2. If in relation to any Collaboration Program, TELETHON-HSR is unable to identify a Lead Vector which meets the Clinical Candidate Selection Criteria within the Research Term, TELETHON-HSR's obligations under this Section 2 shall cease in relation to that *Collaboration Program, unless otherwise agreed by the JSC.*

(ii) *ADA-SCID program*. GSK shall use its Commercially Reasonable Efforts to Develop and obtain Regulatory Approval for the ADA-SCID Product at least in the EU G5 countries and in the U.S., and once Regulatory Approval has been obtained, either in the EU G5 countries or in the U.S., GSK shall use its Commercially Reasonable Efforts to (a) launch and promote to a commercially reasonable extent the ADA-SCID Product, and (b) manufacture and supply the ADA-SCID Product at a sufficient level to meet commercial demand.

(iii) *Other Collaboration Programs*. On a Collaboration Program by Collaboration Program basis, once the PoC Criteria have been met, and if GSK exercises its Option with respect to such Collaboration Program, GSK shall use its Commercially Reasonable Efforts to Develop and obtain Regulatory Approval for the relevant Product at least in the EU G5 countries and in the U.S., and once Regulatory Approval has been obtained, either in the EU G5 countries or in the U.S., GSK shall use its Commercially Reasonable Efforts to (a) launch and promote to a commercially reasonable extent the relevant Product, and (b) manufacture and supply the relevant Product at a sufficient level to meet commercial demand.

(c) GSK Research and Funding Responsibilities.

(i) GSK shall, upon TELETHON-HSR's reasonable request, consult with TELETHON-HSR regarding the Research and Development of Vectors *under each Collaboration Program.*

(ii) As of the Effective Date, GSK shall assume all costs and expenses with respect to the continued Development of the ADA-SCID Program, including CMC costs, including active pharmaceutical ingredient (API) or finished product costs related to any pivotal studies, and all clinical activities, except for any materials that were existing prior to the *Effective Date.*

(iii) Upon the exercise of an Option of a Collaboration Program, GSK shall assume all costs and expenses associated with continuing such Program, including all pre-clinical, clinical development and CMC activities occurring upon and after the exercise of such Option.

2.5 **Milestone Criteria**

(a) *Clinical Candidate Selection Criteria.* Clinical Candidate Selection Criteria shall be consistent with the generic criteria attached in Exhibit A, modified as necessary by the mutual written agreement of the JSC as evidenced by the final mutually approved minutes of the JSC meeting.

(b) *Proof of Concept Criteria.* Prior to the initiation of the first applicable Clinical Trial for a Collaboration Program, the Parties shall through the JSC agree upon the provisional Proof of Concept Criteria for each Collaboration Program, and prior to entering into the relevant Study, the Parties shall agree on the final criteria, subject to GSK's right to have the final say on the matter under Section 3.2(d).

(c) *Proof of Concept Study Design and endpoints*. The JSC shall be responsible for Proof of Concept Study Design and endpoints for each Collaboration Program, subject to GSK's right to have the final say on the matter under Section 3.2(d).

2.6 **Evaluation of Milestone Criteria**

(a) In the event that a Vector achieves all or substantially all of the Milestone Criteria after TELETHON-HSR has completed the activities required to make such an assessment, TELETHON-HSR shall promptly notify GSK in writing of such event and shall provide to the JSC a completed data package containing a set of the analyses, results, raw data, reports and any related correspondence and information received from or sent to any Regulatory Authority from the Collaboration Program for such Lead Vector (the "**Milestone Report**"). Unless otherwise agreed to by the Parties, the JSC will schedule an ad hoc meeting as soon as reasonably possible, but in any event not more than [***] after receipt by GSK of such complete Milestone Criteria Report, to review such Milestone Report and to confirm whether or not such Vector meets all or substantially all of the applicable Milestone Criteria. In the event that the JSC agrees that all or substantially all of the applicable Milestone Criteria have been met, subject to payment of the milestone as outlined in Section 6.2, TELETHON-HSR shall use its Commercially Reasonable Efforts to continue to progress the Collaboration Program through to completion of the Proof of Concept Study.

(b) If all or substantially all of the applicable Milestone Criteria have not been met, then TELETHON-HSR shall complete any additional studies as are required by the JSC to determine if all or substantially all of the applicable Milestone Criteria have been met and if they have, subject to payment of the applicable milestone, progress such Vector through completion of the Proof of Concept Study under the relevant provisions of Articles 2 and 3. If the Parties via the JSC (with neither Party having final say) disagree as to whether or not the relevant Milestone Criteria have been met or can reasonably be achieved for any particular Vector, such dispute will be referred to expert determination in accordance with Section 13.1(b), other than for the achievement of PoC Criteria, for which GSK shall have the final say under Section 3.2(d)(ii).

2.7 **Reports**

TELETHON-HSR shall provide written progress reports on the status of each Collaboration Program, including without limitation, summaries of data associated with TELETHON-HSR's Research and Development activities within the Collaboration Programs and with regards to the jointly undertaken activities with GSK under a Research Program, and the anticipated timelines for carrying out such activities. TELETHON-HSR shall provide such written report to JSC members at least [***] in advance of the applicable JSC meeting. Reports may also be in the format of PowerPoint presentations, datasheets and other similar informal formats.

2.8 **Material Transfer**

To facilitate the conduct of the Programs, either Party may provide to the other Party, at no cost to the other Party, certain biological materials or chemical Vectors, such as cell-based assays or specific Vectors, if available, owned by or licensed to the supplying Party for use by the other Party in furtherance of the Research activities, but not Development, under the Development Plans (such materials or Vectors provided hereunder are referred to, collectively, as "**Materials**"). Except as otherwise provided under this Agreement, all such Materials delivered to the other Party shall remain the sole property of the supplying Party, shall be used only in furtherance of the Programs and expressly in accordance with the applicable Development Plan and solely under the control of the other Party (or its Affiliates), shall not be used or delivered to or for the benefit of any Third Party without the prior written consent of the supplying Party, and shall not be used in Research or testing involving human subjects, unless expressly agreed. The Materials supplied under this Section 2.8 are supplied "as is" and must be used with prudence and appropriate caution in any experimental work, since not all of their characteristics may be known.

2.9 **Regulatory Matters; Compliance**

(a) *Compliance*. Each Party shall use Commercially Reasonable Efforts to conduct all of the Research and Development activities for which it is responsible under the relevant provisions of this Agreement in good scientific manner and, depending on the stage of development, in compliance in all material respects with applicable laws, rules and regulations and all other applicable requirements of cGMP, good laboratory practice and current good clinical practice, and as specifically applicable in accordance with the provisions of this Agreement.

(b) *Data Integrity*.

(i) Each Party acknowledges the importance to the other Party of ensuring that the Collaboration Programs are undertaken in accordance with the following good data management practices:

(A) data are being generated using sound scientific techniques and processes;

(B) data are being accurately and reasonably contemporaneously recorded in accordance with good scientific practices by Persons conducting Research hereunder;

(C) data are being analyzed appropriately without bias in accordance with good scientific practices; and

(D) data and results are being stored securely and can be easily retrieved.

(ii) TELETHON-HSR agrees that it shall use Commercially Reasonable Efforts to carry out the Collaboration Programs and GSK agrees to use Commercially Reasonable Efforts to carry out the GSK Development Programs so as to collect and record any data generated therefrom in a manner consistent with the above requirements as set forth in subsection (a) above.

(c) *Ownership and Transfer of Regulatory Filings and Regulatory Authorizations.*

(i) The Parties acknowledge that, to the extent existing as of the Effective Date, TELETHON-HSR owns all regulatory filings and Regulatory Approvals (including, orphan drug designations) with respect to Products included under the ADA-SCID Program. As soon as reasonably practical after the Effective Date, TELETHON-HSR will transfer and assign ownership of all such regulatory filings and approvals throughout the Territory to GSK (or its designated Affiliate), and send any correspondence to regulatory authorities, execute any instruments, or take any other steps GSK reasonably deems necessary to effectuate such

transfers/assignments to GSK (or its designated Affiliate) throughout the Territory, at which time GSK shall own and be fully responsible for all such regulatory filings and approvals, including any resulting Market Exclusivity Rights, at its own expense, throughout the Territory. An example of the documents and materials to be transferred to GSK is described in Exhibit B.

(ii) Prior to exercise by GSK of its Option over any Collaboration Program, TELETHON-HSR shall own all regulatory filings and Regulatory Approvals (including orphan drug designations) for Products. Upon GSK exercising its Option with respect to a Collaboration Program, TELETHON-HSR shall provide notice in writing to GSK of all such regulatory filings and approvals in the Territory as soon as reasonably practicable for the resulting GSK Development Vectors and Products, including all relevant INDs, if any, and provide GSK with copies of such INDs and other regulatory filings and approvals in the Territory and all pre-clinical and clinical data and results (including pharmacology, toxicology, formulation, and stability studies). Upon exercise of such Option, as soon as reasonably practical thereafter, TELETHON-HSR shall assign and transfer to GSK (or its designated Affiliate), and send any correspondence to Regulatory Authorities, execute any instruments, or take any other steps GSK reasonably deems necessary to effectuate such transfers/assignments to GSK or its designated Affiliate throughout the Territory. GSK (or its designated Affiliate) shall thereafter own and be fully responsible for maintaining all regulatory filings and Regulatory Approvals (including orphan drug designations) and any resulting Market Exclusivity Rights for GSK Development Vectors and Products throughout the Territory. An example of the documents and materials to be transferred to GSK is described in Exhibit B.

(d) *Adverse Event Reporting*. Beginning on commencement of the first Clinical Trial and during the Term of this Agreement, each Party shall promptly inform the other of any Serious Adverse Events related to the Vector or Product that occur in any Collaboration Programs and/or Development Programs and each Party shall provide the JSC with a [***] report summarising

all adverse drug reaction experiences related to any Vectors in a Collaboration Program or a GSK Development Program in connection with the Clinical Trial activities of TELETHON-HSR or GSK, as the case may be, under this Agreement and as required to be reported to the appropriate Regulatory Authorities in the countries in the Territory in which such Vectors are being Developed, in accordance with the appropriate laws and regulations of the relevant countries and Regulatory Authorities in those countries. Through the JSC, GSK and TELETHON-HSR shall have the right to review from time to time the other Party's pharmacovigilance policies and procedures. GSK and TELETHON-HSR agree to cooperate and use good faith efforts to ensure that TELETHON-HSR's adverse event database is organized in a format that is compatible with GSK's adverse event databases. The Parties agree that they will enter into a Pharmacovigilance Agreement within [***] after the Effective Date, or any necessary extension of such period as reasonable agreed to by the Parties.

2.10 **Collaboration Program Costs**

a. TELETHON-HSR shall be responsible for all internal and external costs and expenses associated with the conduct of the Research and Development activities, subject to the provisions of paragraph b of this Section 2.10, under each of the Collaboration Programs, through the earlier of the completion of the Proof of Concept Study or until the exercise of the Option for such Collaboration Program. The costs for those patients who are treated during the time intervening between treatment of the last patient needed for establishing achievement of the PoC Criteria at the time the PoC Option data package is provided to GSK until the date that GSK notifies TELETHON-HSR in writing that it is exercising its Option to the relevant Collaboration Program, will be paid by GSK as an increased cost of the Clinical PoC Option Exercise Fee, and TELETHON-HSR shall add such costs to the Clinical PoC Option Exercise Fee shown in Section 6.2 and shall reflect the total in its invoice to GSK for the Clinical PoC Option Exercise Fee. GSK shall not be obligated to pay any of such costs if it does not exercise its Option with respect to the Collaboration Program.

b. On a Collaboration Program by Collaboration Program basis, in the event that additional costs for a Collaboration Program are required to be incurred by TELETHON-HSR and such additional costs are due to either (i) failure to achieve the PoC Criteria after the completion of the Proof of Concept Study by TELETHON-HSR, where GSK requests and the JSC agrees for TELETHON-HSR to conduct additional pre-clinical or clinical studies aimed at achieving such PoC Criteria, or (ii) based on new regulatory guidelines or requirements from the relevant Regulatory Authorities, additional clinical or pre-clinical studies would need to be conducted by TELETHON-HSR prior to the Option Point, and the JSC agrees that such additional studies are needed, then, in the case of either (i) or (ii), GSK and TELETHON shall share on a [***] basis the costs of such additional studies, in accordance with the following rules:

1. If GSK's portion of such shared costs exceeds [***], then the excess amount paid by GSK in excess of [***] shall be deducted as set out in paragraphs 2 and 3 below.

2. [***] of the excess amount paid by GSK in excess of [***] for its share of costs will be deducted from the Clinical PoC Option Exercise Payment shown in Section 6.2.

3. [***] of the excess amount paid by GSK in excess of [***] for its share of costs will be deducted from the next immediate milestone payment after the Clinical PoC Option Exercise Payment shown in Section 6.2.

2.11 **Subcontracting**

Subject to the terms of this Agreement, each Party shall have the right to engage Affiliates or Third Party academic or non-commercial or commercial fee-for-service subcontractors to perform certain of its obligations under this Agreement pursuant to the Collaboration Programs. Any Affiliate or subcontractor to be engaged by a Party to perform a Party's obligations set forth in the Agreement shall meet the qualifications typically required by such Party for the performance of work similar in scope and complexity to the subcontracted activity. Notwithstanding the preceding, any Party engaging an Affiliate or subcontractor hereunder shall remain principally responsible and obligated for such activities. In addition, each Party engaging a subcontractor with

respect to its obligations under a Collaboration Program shall in all cases (i) retain exclusive Control of any and all intellectual property used with the relevant Party's permission by such subcontractor and (ii) shall obtain exclusive control of any and all intellectual property created by the subcontractor in performance of its obligations directly related to such subcontracted activity under the Collaboration Program and directly related to the composition of matter or method of use of a Vector within such Collaboration Program. The Party engaging a subcontractor under a Collaboration Program shall be solely responsible for all costs associated with obtaining such exclusive Control and rights to such intellectual property. However, it is understood that, in some cases, it may not be commercially reasonable for such Party to obtain such exclusive Control. To the extent that it is not possible to obtain such exclusive Control from any such subcontractor under a Collaboration Program, prior to entering into such arrangement with such subcontractor, such Party shall bring such matter to the JSC for the prior approval of the JSC to enter into such arrangement and for approval by the JSC of the licensing terms and conditions with respect to such arrangement.

3 MANAGEMENT OF THE COLLABORATION

3.1 General Terms for Governance

(a) The Parties will establish a Joint Steering Committee to oversee the clinical Development and Research activities of all the Collaboration Programs, and of the jointly undertaken activities of the Research Program for Vector Manufacturing Improvements and of the jointly undertaken activities of the Research Program for Lentiviral Platform Improvements (the latter two Research Programs are referred to collectively as "The Research Programs"). Decision-Making for all clinical Development and Research activities under the Collaboration Programs will be joint, mutual decision making. In the event of a dispute, final decision making authority will be allocated as follows, after first escalating to the Parties' respective Executive Officers to attempt resolution, and subject always to prior review of any significant safety concerns by the Joint Development Sub-Committee:

For pre-Optioned Collaboration Programs:

- The Parties shall attempt to agree in good faith the development activities, criteria, endpoints, etc. In the event of disagreement, GSK to have final say on the following matters:
    - defining the criteria, design, content and endpoints for PoC;
    - deciding whether PoC has been achieved; and
    - Selecting the Additional Programs.

For the Research Program for Vector Manufacturing Improvements for all activities relating to Development of Vector manufacturing and all related activities:

- The Parties will operate under mutual decision making for jointly undertaken activities and, in the event of a disagreement, GSK will have the final say on the matter.

For the Research Program for Lentiviral Platform Improvements:

- The Parties will operate under mutual decision making for jointly undertaken activities and, in the event of a disagreement, TELETHON-HSR will have the final say on the matter.

(b) The JSC will act only as a conduit for sharing information on all Programs for which GSK has exercised its Option right, and for the ADA-SCID Program. Following exercise of a GSK Option for a Collaboration Program, or as of the Effective Date in the case of the ADA-SCID program, GSK shall manage and be responsible for all the remaining Development and commercialization activities.

(c) For clarity, the Joint Steering Committee responsibilities and authority will only include pre-commercial Research and clinical Development activities for the Collaboration Programs prior to Option exercise by GSK, and for the jointly undertaken activities of the Research Programs. GSK will have sole authority and responsibility for all decisions for a Program following the exercise of an Option and the termination of an ongoing clinical study that

was initiated by Telethon-HSR prior to the Option Point, and in the case of the ADA-SCID Program, from the Effective Date forward. It is anticipated, and if agreed in writing in advance by GSK via the JSC, that TELETHON-HSR may remain responsible for and sponsor, provided, however, that GSK shall have final say on all aspects of the conduct and progression of the Program after exercise of the Option right. GSK will have full control, sole decision-making authority and responsibility for the commercialization of and all commercial activities in the Territory for all "Licensed Products" resulting from all Programs.

3.2 **Joint Steering Committee**

Promptly and in any event within [***] after the Effective Date, the Parties shall establish a joint steering committee (the "**Joint Steering Committee**" or **"JSC"**) as more fully described in this Section 3.2. The JSC shall initially have advisory, oversight and decision-making responsibilities for all Research and Development activities performed under the Collaboration Programs. Upon completion of the Research Term, or upon Option exercise by GSK, on a Program-by-Program basis, the role of the JSC will shift from an oversight and decision-making body to a vehicle used to facilitate information exchange between the Parties regarding the GSK Development Programs, as further described below. Each Party agrees to keep the JSC informed of its progress and activities under the Programs.

(a) *Membership*. The JSC shall be comprised of [***] representatives (or such other number of representatives as the Parties may agree) from each of GSK and TELETHON-HSR. Each Party shall provide the other with a list of its initial members of the JSC no later than [***] prior to the first scheduled meeting of the JSC, which shall be no later than [***] after the Effective Date. Each Party may replace any or all of its representatives on the JSC at any time upon written notice to the other Party in accordance with Section 13.7 of this Agreement. Each representative of a Party shall have relevant expertise (either individually or collectively) in biopharmaceutical drug discovery and/or development. Any member of the JSC may designate a substitute to attend and perform the functions of that member at any meeting of the JSC. Each Party may, in its reasonable discretion, invite non-member

representatives of such Party to attend meetings of the JSC as non-voting participants, subject to the confidentiality obligations of Article 9. The Parties shall designate a chairperson (a "**Chairperson**") to oversee the operation of the JSC, each such Chairperson to serve a [***] term. The right to name the Chairperson shall alternate between the Parties, with TELETHON-HSR designating the first such Chairperson.

(b) *Meetings*. During the Research Term, the JSC shall meet in person or otherwise at least once each [***] (with at least [***] in-person meeting per year), and more or less frequently as the Parties mutually deem appropriate, on such dates and at such places and times as provided herein or as the Parties shall agree. Upon conclusion of the Research Term, the JSC shall meet, in person or otherwise, at least once every [***] to provide TELETHON-HSR an update regarding GSK's efforts to Develop and commercialize Vectors and GSK Products in the GSK Development Programs, including without limitation, material changes in the GSK Development Plans for GSK Products, status of regulatory filings, anticipated indications, anticipated launch dates, manufacturing issues, and the like. Meetings of the JSC that are held in person shall alternate between the offices of the Parties, or such other place as the Parties may agree. The members of the JSC also may convene or be polled or consulted from time to time by means of telecommunications, video conferences, electronic mail or correspondence, as deemed necessary or appropriate. Each Party will bear all expenses it incurs in regard to participating in all meetings of the JSC, including all travel and living expenses.

(c) *Minutes*. Each Party shall nominate an Alliance Manager, and the Alliance Managers of the Parties will equally share and be responsible for preparing and circulating minutes of each meeting of the JSC, setting forth, *inter alia*, an overview of the discussions at the meeting and a list of any actions, decisions or determinations approved by the JSC and a list of any issues to be resolved by the Executive Officers pursuant to Section 3.1(a). Such minutes shall be effective only after approval by both Parties. With the sole exception of specific items of the meeting minutes to which the members cannot agree and that are escalated to the Executive Officers as provided in Section 3.1(a),

definitive minutes of all JSC meetings shall be finalized no later than [***] after the meeting to which the minutes pertain. If at any time during the preparation and finalization of the JSC minutes, the Parties do not agree on any issue with respect to the minutes, such issue shall be resolved by the escalation process as provided in Section 3.1(a). The decision resulting from the escalation process shall be recorded by the Alliance Manager in amended finalized minutes for such meeting.

(d) *Decisions*.

(i) Except as otherwise provided for herein, the JSC shall have oversight authority and responsibility over matters and decisions relating to Research and Development for each Collaboration Program and for each of the Research Programs up until the conclusion of the Research Term, at which time oversight and decision-making authority regarding the GSK Development Programs that were subject to JSC oversight shall be transferred to GSK. Except as otherwise provided herein, with respect to a given Collaboration Program or GSK Development Program, or with respect to the Research Programs, all decisions of the JSC shall be made by unanimous agreement of the JSC, with each Party having [***]. Except as otherwise expressly provided in the provisions of Article 2 or in Section 3.1 or in Section 3.2 (d)(ii) below, or otherwise in this Article 3, any disagreement in relation to any matter which is governed by the JSC shall be resolved as follows: (i) for any matters arising prior to the exercise of an Option by GSK for a Collaboration Program, TELETHON-HSR shall have the final decision-making authority and (ii) for any matters arising after the exercise of an Option by GSK for a Collaboration Program, GSK shall have the final decision-making authority. The final decision-making authority of a Party shall not be subject to dispute resolution under Section 13.1 or 13.2.

(ii) Notwithstanding the foregoing, GSK shall have final decision-making authority with respect to the Proof of Concept Criteria and the Proof of Concept Study Design and Proof of Concept Study end points for all Collaboration Programs, and with respect to whether or not the PoC Criteria have been achieved, and the selection of the Additional Programs.

(e) *Responsibilities*. The JSC shall perform the following functions and have the following responsibilities and authority with respect only to the Collaboration Programs, and not the ADA-SCID Program, and shall be subject to the final decision-making authority of the respective Parties as set forth above in Section 3.2(d), some or all of which may be addressed directly at any given meeting of the JSC:

(i) review and comment on the Development Plan for each Collaboration Program and monitor progress of activities under such Development Plan;

(ii) oversee and guide the progress of each Collaboration Program in accordance with the applicable Milestone Criteria;

(iii) prepare, review, modify, update and approve each Milestone Criteria, Milestone Report and Proof of Concept Study Design;

(iv) assess the Proof of Concept Criteria for each Collaboration Program;

(v) determine that a Product or Vector (as the case may be) has satisfied the applicable Milestone Criteria;

(vi) except as otherwise provided in Section 3.1(h) below, discuss and attempt to resolve any deadlock issues submitted to it by any Subcommittee (as defined in Section 3.1(g)), in accordance with the procedures established in Section 3.1(d);

(vii) serve as an information transfer vehicle, from time to time, to facilitate the discussion of Development and commercialization of GSK Products under GSK Development Programs;

(viii) periodically review the Development and commercialization of any GSK Product and GSK Development Plan and discuss any comments with GSK; and

(ix) such other responsibilities as may be assigned to the JSC pursuant to this Agreement or as may be mutually agreed upon by the Parties from time to time.

(x) Either Party may present a proposed Additional Program to the JSC for consideration as a Collaboration Program hereunder, and GSK will have final say on selecting any Additional Program for inclusion hereunder as a Collaboration Program. If selected, such proposed program will become an Additional Program and thus a new Collaboration Program, and GSK will pay the milestone payments for such Additional Program as described under Section 6.2.

(xi) In the event that GSK is to initiate a lentiviral ADA-SCID Program within the Field during the Research Term, it shall first offer TELETHON-HSR the opportunity to pursue such Program as an Additional Program hereunder.

For clarity, the JSC shall not have any authority beyond the specific matters set forth above in this Section 3.1(e), and in particular shall not have any power to amend or modify the terms or provisions of this Agreement. In addition, GSK (and not TELETHON-HSR or the JSC) shall have the sole right to make decisions with respect to (A) the exercise of an Option; or (B) subject to GSK's diligence obligations in Section 5.1(c), the Research, Development, progression, manufacture, and commercialization of any Vectors or Products under a GSK Development Program.

(f) *Subcommittee(s).* From time to time, the JSC may establish subcommittees to oversee particular projects or activities, as it deems necessary or advisable (each, a "**Subcommittee**"). Each Subcommittee shall consist of such number of members as the JSC determines is appropriate from time to time. Such members shall be individuals with expertise and responsibilities in the areas of pre-clinical development, clinical development, patents, process sciences, manufacturing, regulatory affairs, product development and/or product commercialization, as applicable to the stage of development of the project or activity.

(g) *Joint Patent Subcommittee*. Within [***] after the Effective Date, the JSC shall establish a Subcommittee (the **"Joint Patent Subcommittee"** or **"JPS"**) to be responsible for the coordination of the Parties' efforts in accordance with Article 8 of this Agreement, including the preparation, review and filing of patent applications and assessments of inventorship of inventions created during the Research Term under the Collaboration Programs, and the assessment of the appropriateness of filing divisional patent applications. The JPS shall be comprised of an equal number of representatives from each of GSK and TELETHON-HSR and shall meet on such dates and at such places and times agreed to by the Parties. All decisions of the JPS on matters for which it has responsibility shall be made by consensus, with each Party having collectively [***] vote in all decisions. In the event that the JPS is unable to reach a consensus decision within [***] after it has met and attempted to reach such decision, then either Party may, by written notice to the other, have such issue submitted to the chief patent counsel of GSK and of TELETHON-HSR (together, the **"Chief Patent Counsel"**), or such other person holding a similar position designated by GSK or TELETHON-HSR (who may be a Third Party) from time to time, for resolution. The Chief Patent Counsel shall meet promptly to discuss the matter submitted and to determine a resolution. Prior to exercise of an Option for a Collaboration Program, if the Chief Patent Counsel are unable to determine a resolution in a timely manner: (i) with respect to all patent matters relating TELETHON-HSR Patent Rights and to Joint Patent Rights owned jointly by TELETHON-HSR and GSK and related to such Program prior to exercise by GSK of its Option, then the

decision of the Chief Patent Counsel of TELETHON-HSR shall be binding upon the Parties without further review, and (ii) with respect to all patent matters relating TELETHON-HSR Patent Rights and to Joint Patent Rights and related to such Program after exercise by GSK of its Option, then the decision of the Chief Patent Counsel of GSK shall be binding upon the Parties without further review. Each Party will bear all expenses it incurs in regard to participating in all meetings of the JPS, including all travel and living expenses. In addition, the Parties will discuss within the Joint Patent Subcommittee any Third Party licences that are necessary or desirable for activities under the Collaboration Programs, the ADA-SCID Program or under jointly undertaken activities of the Research Programs, and shall reasonably cooperate in good faith to endeavour to obtain the most favourable conditions and the broadest license scope achievable for both Parties.

(h) *Joint Development Sub-Committee.* Within [***] of a Lead Vector achieving the Clinical Candidate Selection Criteria the Parties will establish a joint development committee comprised of personnel with relevant expertise to oversee the Development of the Lead Vector.

(i) *Review of Safety Issues at the Joint Development Sub-Committee*. The Parties will discuss and consider at the Joint Development Sub-Committee any significant safety concerns expressed by one Party to the other Party, and will facilitate via the Joint Development Sub-Committee escalation to internal safety Review Boards of each Party, where appropriate. The Parties agree to cooperate in good faith to resolve in a timely manner and to a mutually acceptable resolution, any significant and material safety concerns raised, including, without limitation, the decision as to whether or not to enter into any first time in humans clinical studies when one Party has raised significant safety concerns, or any safety concerns of GSK regarding any monitoring or study protocols established by TELETHON-HSR for first time in humans studies. If both Parties mutually agree via the Joint Development Sub-committee, the Program may be mutually terminated pursuant to article 12.3(b). In the event the Joint Development Sub-Committee cannot resolve a safety dispute within [***], it will escalate the dispute to the Executive Officers designated by both Parties. If not resolved by the Executive Officers within an additional [***], the Party raising the compelling safety issue and desiring to terminate the Program will have the right to unilaterally terminate the Collaboration Program in accordance with the terms and conditions of Section 12.3(b).

3.3 **Alliance Managers**.

Promptly after the Effective Date, each Party shall appoint an individual (who may not be an existing member of the JSC) to act as alliance manager for such Party (each, an "**Alliance Manager**"). Each Alliance Manager shall thereafter be permitted to attend meetings of the JSC as a non-voting observer, subject to the confidentiality provisions of Article 9. The Alliance Managers shall be the primary point of contact for the Parties regarding the activities contemplated by this Agreement and shall facilitate all such activities hereunder including, but not limited to, the exchange of information and Know-How described in Section 2.8. The Alliance Managers shall also be responsible for assisting the JSC and any of its Sub-Committees in performing its oversight responsibilities. The name and contact information for each Party's Alliance Manager, as well as any replacement(s) chosen by TELETHON-HSR or GSK, in their sole discretion, from time to time, shall be promptly provided to the other Party in accordance with Section 13.8 of this Agreement.

3.4 **[***]**

4 GRANT OF RIGHTS

4.1 **License Grant to GSK for the ADA-SCID Program**

Subject to the terms and conditions of this Agreement, TELETHON-HSR hereby grants to GSK, and GSK hereby accepts and shall have with effect from the Effective Date, an exclusive (even as to TELETHON-HSR and its Affiliates), worldwide, sublicenseable (subject to Section 4.14) license in the Territory under all of TELETHON-HSR's and its Affiliates' rights, title and interest in and to the ADA-SCID Program EXCLUSIVELY LICENSED IP to make, have made, use, sell, offer for sale and import Vectors and Products included under or resulting from the ADA-SCID Program as and into GSK Products in the Field.

4.2 **GSK Options, Exercise of Options and Resulting Licenses**

(a) *Grant of Option Rights*. Subject to the terms and conditions of this Agreement, TELETHON-HSR hereby grants to GSK with respect to each Collaboration Program the exclusive option during the Research Term, which shall be exercisable on a Collaboration Program-by-Collaboration Program basis at GSK's sole discretion, to obtain the exclusive license set forth in Section 4.2(c) (each, an "**Option**"), subject to the terms and conditions described in Sections 4.2(b)—4.2(d) below. GSK shall be limited to exercising [***] Option per Collaboration Program, and on exercise of an Option and payment of the applicable Option Exercise Fee set out in Section 6.2, GSK shall have exclusive rights to such Collaboration Program consisting of all Vectors and Products under a given Collaboration Program.

(b) *Option Period*. The Option may be exercised on a Collaboration Program-by-Collaboration Program basis at any time during the Research Term starting on the Option Period Start (defined in Section 4.2(d) below) and ending when the Review Period (defined in Section 4.2(d) below) expires.

(c) *Upon Exercise of Option - Grant of Exclusive License to GSK*. Subject to the terms and conditions of this Agreement, upon GSK's exercise of the relevant Option with respect to a given Collaboration Program in accordance with Section 4.2(d) or by operation of Section 12.5 and TELETHON-HSR's receipt of the applicable Option Exercise Fee, TELETHON-HSR and its Affiliates shall be hereby deemed to have granted and hereby grant to GSK, conditional upon such event, an exclusive, worldwide, sublicenseable (subject to Section 4.14) license (which rights shall be exclusive even as to TELETHON-HSR and its Affiliates), in the Territory under all of TELETHON-HSR's and its Affiliates' rights, title and interest in and to the relevant Collaboration Program Exclusively Licensed IP to make, have made, use, sell, offer for sale and import Vectors and/or Products included under or resulting from the Collaboration Program as and into GSK Products in the Field.

(d) *Exercise of Option.*

(i) The "Option Period Start" with respect to a Collaboration Program will commence upon the receipt by GSK of the Milestone Report for the Proof of Concept Study or as otherwise agreed or upon GSK's right to exercise its Option early arising in accordance with Section 4.2(d)(ii) or 4.8(a) below or Section 12.5(c) below. TELETHON-HSR will, in order to enable GSK to determine whether or not to exercise an Option, provide access to the TELETHON-HSR data room containing the set of material or relevant clinical and preclinical information related to the applicable Collaboration Program. GSK shall decide whether or not to exercise the Option and may exercise the Option with respect to a Collaboration Program by written notice to TELETHON-HSR at any time within [***] after the Option Period Start (the "Review Period"), unless extended by the mutual written agreement of the Parties. Upon GSK's exercise of an Option and receipt by TELETHON-HSR of the applicable Option Exercise Fee set forth in Section 6.2, the Collaboration Program will become a GSK Development Program. Subject to Section 5.3(b), any Option exercise shall be irrevocable.

(ii) Early Exercise of Option. GSK may, on a Collaboration Program-by-Collaboration Program basis, at any time during the Research Term after the [***] have been treated under such Collaboration Program, exercise early any unexercised Option on a Collaboration Program-by-Collaboration Program basis by providing written notice to TELETHON-HSR and paying the Option Exercise Fee and all other milestones payments and royalty payments as and when they become due to TELETHON-HSR in accordance with Article 6. Following such early exercise of an Option, GSK shall be responsible for all costs of the Program that is the subject of such Option.

4.3 **Non-Exclusive license to GSK for the conduct of its Obligations under a Collaboration Program prior to Option exercise.**

Prior to the exercise by GSK of its Option, on a Collaboration Program-by-Collaboration Program basis, TELETHON-HSR shall grant and GSK shall have a fully-paid and royalty-free, worldwide, non-exclusive license under all existing (as of the Effective Date) and

arising (during the Term of the Agreement) TELETHON-HSR Patents and Joint Patents and TELETHON-HSR Know-How and Joint Know-How relating to the Collaboration Program or included under the Lentiviral Platform Improvements IP or the Vector Manufacturing Improvements IP, as is necessary or useful for GSK and/or its Affiliates to carry out its activities and obligations with respect to the relevant Collaboration Program for GSK's internal research and development purposes pursuant to this Agreement only.

4.4 **GSK's First Right to Negotiate for Broader Licenses.**

In addition to the licenses and Options granted to GSK above, and where not precluded by any existing or new agreement between TELETHON-HSR and a Third Party, GSK shall have the first right to negotiate in good faith and on commercially-reasonable terms, a non-exclusive, worldwide license, under all of TELETHON-HSR's and/or its Affiliate's rights therein, to use the Lentiviral Platform Improvements IP and/or the Vector Manufacturing Improvements IP, for any of GSK's and/or its Affiliate's research, development or commercial purposes, beyond the scope of the Programs hereunder or beyond the Alliance Scope. The commencement of the period of time for any such license negotiation will be, in the case of patent applications as the subject matter to be licensed, the filing date of a TELETHON-HSR owned patent application, and for TELETHON-HSR Know-How that is not the subject of a patent application, will be the date that GSK first requests additional information from TELETHON-HSR regarding any such TELETHON-HSR Know-How that is discussed or disclosed to GSK at or through the JSC or JPS. GSK shall have a period of [***] from the date that it receives the additional information requested from TELETHON-HSR further describing such Know-How in order to determine if it wants to exercise its right to negotiate such a license. In the case of patent applications, GSK will have [***] from the date it first receives a copy of such patent application to evaluate the patent application and to communicate the intention to start negotiations. If GSK does not exercise its rights within such [***] period then TELETHON-HSR shall be free to negotiate for such license outside of the Alliance Scope with Third Parties. Therefore, TELETHON-HSR shall be obligated to disclose in good faith all such additional information requested by GSK, and the related Know-How and patent applications to GSK at the JSC or at the JPS.

4.5 **Licenses of Jointly Owned IP by TELETHON-HSR and Third Parties.**

Where relevant and not precluded by Third Party agreements and not already granted to GSK under Section 4.1 or 4.2, TELETHON-HSR shall in good faith and with reasonable efforts negotiate with the relevant Third Party the right to grant to GSK for the purpose of the Development and commercialization of Products resulting from the ADA-SCID Program or the Collaboration Programs: (a) either an exclusive license under TELETHON-HSR's share of Joint IP that is owned jointly between TELETHON-HSR and such Third Party, such license to be granted at no additional cost to GSK, or, if not possible, (b) a non-exclusive license under TELETHON-HSR's share of Joint IP that is owned jointly between TELETHON-HSR and such Third Party, such license to be granted at no additional cost to GSK.

4.6 **Covenants of Telethon relating to Licenses to Third Parties under Joint IP beyond the Alliance Scope**

(a) In addition to the license and Option rights granted to GSK above, for any Vector Manufacturing Improvements IP which is invented/owned jointly by GSK and TELETHON-HSR, TELETHON-HSR hereby agrees and covenants not to license or sublicense or assign or transfer its rights therein outside of the scope of the Programs or outside of the Alliance Scope to any for-profit or commercial entity without GSK's prior written consent, such consent not to be unreasonably withheld in the event that GSK is not practicing such technology.

(b) In addition to the license and Option rights granted to GSK above, for any Lentiviral Platform Improvements IP which is invented/owned jointly by GSK and TELETHON-HSR, TELETHON-HSR hereby agrees and covenants not to license or sublicense or assign or transfer its rights therein outside of the scope of the Programs or outside of the Alliance Scope to any for-profit or commercial entity without GSK's prior written consent, such consent not to be unreasonably withheld in the event that GSK is not practicing such technology.

4.7 **Third Party Patents on the Lentiviral Platform.**

If any licences under a Third Party's patents with respect to the lentiviral platform are necessary or desirable, as determined by either Party or by the JPS, for the Development and/or commercialization of Vectors or Products under or resulting from the relevant Program or for the conduct of the alliance hereunder within the Alliance Scope, including the Research Programs as well as the Collaboration Programs, then GSK and/or TELETHON, as appropriate and as determined by the JPS, shall cooperate in good faith and with reasonable efforts to negotiate with the relevant Third Parties for the necessary or desirable licenses that will, wherever reasonably obtainable, include the right to sublicense to the other Party for research and development purposes for the furtherance of the relevant Programs hereunder.

4.8 ***(a) Change of Control of TELETHON-HSR.***

A "Change of Control Event" in relation to TELETHON-HSR shall be deemed to have occurred if either (a) F. Telethon or F. San Raffaele withdraws entirely from the TIGET joint project or withdraws all or substantially all of its funding support from the TIGET joint project, or (b) a Third Party acquires the right to control and direct the TIGET joint project. In the event that a Change of Control Event occurs in relation to TELETHON-HSR;

(i) if such Change of Control Event occurs prior to the exercise of the Option for a Collaboration Program, GSK shall have the right to exercise such Option immediately at its sole discretion except that the Option Payment set forth in Section 6.2(b) shall be paid in [***] equal installments, with the first installment paid upon exercise of the Option, and the remaining installment paid upon completion of the next milestone point set forth in Section 6.2(b), and GSK shall have the right to terminate the Agreement in the event of a Change of Control Default as set out below.

(ii) If the Change of Control Event occurs in relation to TELETHON-HSR as defined above following exercise of the Option for any Collaboration Program, then, within [***] after the Change of Control Event, and every [***] thereafter for the [***], the Parties, or the Parties and the Third Party acquiror, as the case may be, shall meet to discuss, in good faith and in as much detail and specifics as is practicable at the time, the consequences of

such Change of Control Event under this Agreement. If at any time in the [***] following the Change of Control Event to which either Section 4.6(i) or 4.6(ii) above applies, GSK has a reasonable, good faith basis to believe, based on the plans, documents, actions or inactions of TELETHON-HSR and/or its acquiror that TELETHON-HSR and/or its acquiror has not or will not, with respect to any Program, employ diligent efforts that are at least equivalent to the diligent efforts that were employed by TELETHON-HSR for the Program prior to such Change of Control Event (but excluding any period of delay or disruption due to such Change of Control Event being pending), then GSK shall provide written notice to TELETHON-HSR, such notice to allege the specific basis for GSK's view that the diligent efforts are not being or will not be applied to the Program (a "Change of Control Default"). TELETHON-HSR and/or its acquiror shall notify GSK whether or not it plans to cure such deficiency, and if it so elects to cure, shall produce a plan within [***] of GSK's notice to cure any such deficiencies in efforts or resources so alleged by GSK. In the event that TELETHON-HSR notifies GSK that it does not intend to cure such deficiencies or GSK reasonably believes that such deficiency has not been corrected or cured within a [***] period following GSK's notice (the "Change of Control Default"), GSK shall have the right to exercise its Options to any and all Collaboration Programs, at GSK's sole discretion, by providing written notice to TELETHON-HSR within thirty (30) Calendar Days after such cure period has expired or such notice from TELETHON-HSR or its acquiror that it does not intend to cure such deficiencies. In the event of a dispute between the Parties as to whether or not any such deficiency has been cured or as to whether or not any such deficiency exists at all, the Parties shall refer the matter to arbitration in accordance with Section 13.2 below.

(iii) Financial Consequences for Change of Control Default. Upon the exercise by GSK of its Option to a Collaboration Program, pursuant to Section 4.2 and due to a Change of Control Default, the Option Exercise Fee (which shall be payable immediately on exercise of the Option) and all the applicable milestone payments and royalty payments as they become due under Article 6 shall all be reduced as follows, and the Bonus milestone payments under Section 6.2 shall not be payable, on a Program-by-Program basis for each Collaboration Program with respect to which GSK exercises its Option as follows:

1) if Option exercise occurs for a Collaboration Program with a Lead Vector that has not yet satisfied the Clinical Candidate Selection Criteria, then the Option Exercise Fee, future milestone payments, and royalty payments payable under Section 6 shall all be reduced by [***];

2) if Option exercise occurs for a Collaboration Program with a Lead Vector that has satisfied the Clinical Candidate Selection Criteria but prior to initiation of the Proof of Concept Study then the Option Exercise Fee, future milestone payments, and the royalty payments payable under Section 6 shall all be reduced by [***];

3) if Option exercise occurs for a Collaboration Program after the initiation of a Proof of Concept Study for such Program, but before completion of the Proof of Concept Study then the Option Exercise Fee shall be reduced by [***] but all other milestone payments and royalty payments shall be payable under Section 6 in full as though GSK had exercised its Option after the Proof of Concept Study.

(iv) In the event of any Change of Control Event of TELETHON-HSR except as expressly set forth in this Section 4.8 (a), the rights and obligations under this Agreement of each Party, including any successor to TELETHON-HSR, shall remain unchanged and in full force and effect and shall bind TELETHON-HSR and its successor, as the case may be.

(b) ***Change of Control of GSK.*** A "Change of Control Event" in relation to GSK shall be deemed to have occurred if GSK: (a) merges or consolidates with any other Person (other than an Affiliate or wholly-owned subsidiary not created for the purpose of such merger or consolidation of GSK with a Third Party); or (b) effects any other transaction or series of transactions (other than a listing on a public recognised stock exchange or fund raising from existing or new investors in the ordinary course of business), such that the stockholders of GSK immediately prior thereto, in the aggregate, no longer own, directly or indirectly, beneficially or legally, at least [***] of the outstanding voting securities or capital stock of the surviving entity following the closing of such merger, consolidation, other transaction or series of transactions. If a Change of Control Event occurs in relation to GSK following the exercise of an Option for any Program, then within [***] after the Change of Control Event, and every [***] thereafter for the first [***] quarters, the Parties and the acquiror shall meet to discuss, in good faith and in as much detail and specifics as is practicable at the time, the consequences of such Change of Control Event under this Agreement. If at any time in the [***] months following the Change of Control Event, TELETHON-HSR has a reasonable, good faith basis to believe, based on the plans, documents, actions or inactions of GSK and/or its acquiror that GSK and/or its acquiror has not or will not, with respect to any Program, employ Commercially Reasonable Efforts that are at least equivalent to the Commercially Reasonable Efforts that were employed by GSK for the GSK Development Program prior to such Change of Control Event (but excluding any period of delay or disruption due to such Change of Control Event being pending), then TELETHON-HSR shall provide written notice to GSK, such notice to allege the specific basis for TELETHON-HSR's view that the diligent efforts are not being or will not be applied to the Program. GSK and/or its acquiror shall notify TELETHON-HSR whether or not it plans to cure such deficiency, and if it so elects to cure, shall produce a plan within [***] of TELETHON-HSR's notice to cure any such deficiencies in efforts or resources so alleged by TELETHON-HSR. In the event that GSK notifies TELETHON-HSR that it does not intend to cure such deficiencies or TELETHON-HSR reasonably believes that such deficiency has not been corrected or cured within a [***] period following TELETHON-HSR's notice, TELETHON-HSR shall have the right to terminate any and all GSK Development Programs that are deficient, at TELETHON-HSR's sole discretion, by providing written notice to GSK within [***] after such cure period has expired or such notice from GSK or its acquiror that it does not intend to cure such deficiencies. In the event of a dispute between the Parties as to whether or not any such deficiency has been cured or as to whether or not any such deficiency exists at all, the Parties shall refer the matter to arbitration in accordance with Section 13.2 below.

4.9 ***Expiration or Termination of Option***.

If GSK does not exercise the Option with respect to a particular Collaboration Program within the applicable Option Review Period described above or GSK elects not to exercise the Option, then, the Option shall terminate with respect to such Collaboration Program, which shall become a TELETHON-HSR Development Program, and TELETHON-HSR will thereafter have all rights, itself or with or through an Affiliate or Third Party, (a) to Develop and commercialize all Vectors and Products within the Collaboration Program and (b) to use any data, regulatory filings and know-how generated or used in the course of the Collaboration Program as further set forth in Section 5.2. Any Joint IP that is jointly owned between TELETHON-HSR and GSK will be licensed exclusively to TELETHON-HSR in accordance with the terms and conditions stated in Section 5.2. TELETHON-HSR will have the right to negotiate with GSK in good faith and on commercially reasonable terms for a license to use the relevant solely owned GSK IP solely for the Development and commercialization of the Products under the relevant Collaboration Program for which GSK has declined to exercise its Option as set forth in Section 5.2. The non-exclusive license granted to GSK under Section 4.3 for GSK's research and development purposes pursuant to the relevant Collaboration Program using TELETHON-HSR solely owned IP will be terminated.

4.10 **HSR and Equivalent Foreign Laws**.

If GSK reasonably determines in good faith prior to the expiration of the Review Period for exercise of an Option for a Particular Collaboration Program that the exercise of such an Option is required to be filed with the Federal Trade Commission (the "**FTC**") under the Hart-Scott-Rodino Antitrust Improvements Act of 1976 (15 U.S.C. §18a) ("**HSR**") or with equivalent foreign governmental authorities under any similar foreign law, GSK shall provide written notice of exercise of the Option to TELETHON-HSR prior to the end of the Review Period, which notice shall include GSK's binding commitment to complete the exercise of the Option, subject only to HSR or other governmental

clearance by the FTC or other governmental authority, and the Review Period automatically shall be extended for [***] (the "**Review Period Extension**"). If the exercise of the Option does not comply with the requirements of Section 4.2 and this Section 4.10, including, for example, because it includes other conditions to the completion of the exercise of the Option other than the grant of HSR or other governmental clearance, then the Parties shall negotiate in good faith to determine an appropriate way to proceed. If HSR or other governmental clearance is not granted within the Review Period Extension, or if GSK receives a "Second Request" from the FTC or similar request for additional information from a governmental authority in connection with such filing, the Review Period Extension shall be extended for an additional period of time as reasonably needed (which additional period is not expected to exceed an additional [***] unless reasonably required to obtain clearance) to permit GSK to obtain FTC or other governmental clearance or to respond to the Second Request or provide additional information to the governmental authority. If GSK elects not to respond to the Second Request or to withdraw its request for HSR or other governmental clearance or HSR, the Option shall terminate, and TELETHON-HSR shall have the same rights as are set forth in Section 4.2(d) in respect of the Vectors resulting from the applicable Collaboration Program. If HSR or other governmental clearance has not been granted by the end of the extended Review Period Extension, TELETHON-HSR and GSK shall promptly meet to discuss in good faith whether an additional extension of the Review Period Extension is reasonable under the circumstances, and to discuss and consider in good faith, where appropriate, the renegotiation of their financial and other obligations under the Agreement with respect to the affected Program, with the objective of placing each Party, to the maximum extent possible, in the same economic position that each Party would have occupied if the Program in question had not been included in the Agreement from the beginning as of the Effective Date. Notwithstanding the foregoing, nothing in this paragraph or the Agreement shall require either Party to divest any assets in such Party's ownership or Control as of the Effective Date. GSK shall be solely responsible for all reasonable costs and expenses of either Party in connection with the grant of any exclusive license to GSK hereunder (including all governmental filing or other fees, and any other costs and expenses) arising from pursuing or obtaining any HSR approval.

4.11 ***Tolling of Payment Obligations***.

If the exercise by GSK of any Option or the grant to GSK of any exclusive license under Article 4 of this Agreement requires or required prior to the same the making of filings under HSR, or under any similar premerger notification provision in the European Union or any other jurisdiction, then all rights and obligations related to the exercise of such Option or to the grant of such exclusive license (including the payment of any Option Exercise Fee or the payment of any other applicable payment or milestone) shall be tolled until the applicable waiting period has expired or been terminated or until approval or clearance from the reviewing authority has been received, and each Party agrees to cooperate at the request of the Party which decides in its sole discretion to respond to any such request for information to expedite review of such transaction. In the event that HSR clearance is not reasonably achievable within [***] from notification, the Parties shall discuss in good faith potential alternatives, including termination of the relevant Program or the Agreement, as may be mutually agreed between the Parties in good faith, and, where appropriate, to discuss and consider in good faith the renegotiation of their financial and other obligations under the Agreement with respect to the affected Program, with the objective of placing each Party, to the maximum extent possible, in the same economic position that each Party would have occupied if the Program in question had not been included in the Agreement from the beginning as of the Effective Date.

4.12 ***No Grant of Rights to Third Parties***.

Until such time as the Review Period (as may be extended), for an Option granted to GSK pursuant to Section 4.2 with respect to a given Collaboration Program has expired or terminated (including, for example, because the JSC agrees that a Collaboration Program be terminated), TELETHON-HSR and its Affiliates shall not grant to any Third Party rights in or to any Exclusively Licensed IP that are inconsistent with or that would interfere with the grant of the licenses that may result from the exercise of such Option by GSK hereunder. For the avoidance of doubt, the Parties understand and agree that for so long as an Option is in effect, such Option shall be exclusive as to the Vectors that are the subject of the relevant Collaboration Program, and TELETHON-HSR and its Affiliates shall have no right to offer or negotiate with any Third Party with respect to the grant to such Third Party of any right or license, or with respect to any settlement, consent judgment or other disposition of any action or proceeding under Article 8, or with respect to any other encumbrance of any kind, in or to any of such Vectors or any Exclusively Licensed IP that would interfere with the grant of the licenses resulting from the exercise of such Option to GSK hereunder. The grant of the Options by TELETHON-HSR hereunder is irrevocable except as expressly provided under Article 12.

4.13 ***Sublicensing***.

In the event GSK intends to grant a sublicense to a Third Party under the licences granted in this Article 4, GSK shall provide written notice of such proposed sublicense (including the identity of the Third Party Sublicensee), to TELETHON-HSR. GSK shall ensure that such sublicenses are granted on terms which are consistent with this Agreement and GSK shall remain liable for the performance of the obligations under this Agreement of its Sublicensees in connection with the grant of such sub-licensed rights.

4.14 **Technology Transfer after Option Exercise**

As soon as reasonably practicable after GSK exercises its Option for a Collaboration Program pursuant to Section 4.2, TELETHON-HSR shall deliver to GSK, at no cost to GSK, all Know-How and material in its possession and Control relating to the Vectors and Products in such Collaboration Program, and the documents and materials that are described in Section 2.9 (c), as exemplified in Exhibit B, and any other such information as may be in TELETHON-HSR's Control and in the possession of any subcontractors (including Third Party manufacturers) appointed by TELETHON-HSR under Section 2.11, in each case in a format to be agreed between the Parties but which is in an electronically editable format suitable for eCTD submission. TELETHON-HSR shall provide such technology transfer services as may be reasonably necessary to transfer the Vector manufacturing processes to GSK's or GSK's Third Party manufacturer's site. TELETHON-HSR shall use Commercially Reasonable Efforts with respect to those activities for which it is responsible to ensure orderly transition and uninterrupted Development of the GSK Development Program.

5 POST-EXERCISE and POST-LICENSE ACTIVITIES

5.1 GSK Development and Commercialization

(a) GSK, either itself and/or by and through its Affiliates, Sublicensees or contractors, shall be responsible for all Research, Development, regulatory, manufacturing, marketing, advertising, promotional, launch and sales and other commercial activities in connection with Vectors and Products resulting from the Programs.

(b) Except as expressly stated in Section 3.2(d), GSK shall have sole and final decision-making authority with respect to the Research, Development, progression, regulatory activities, manufacturing, marketing, sales and other commercialization activities for any Vectors or Products within a GSK Development Program, without submitting any such matter for review or decision to the JSC or Executive Officers.

(c) GSK Diligence: Upon GSK's exercise of an Option with respect to a Collaboration Program, and as of the Effective Date for the ADA-SCID Program, GSK shall submit to the JSC the relevant GSK Development Plan as defined in letter (d) of this article 5.1. On a Program-by –Program basis, as a condition for GSK maintaining the exclusive license granted to GSK under Article 4 with respect to a particular GSK Development Program, GSK shall use its Commercially Reasonable Efforts to Develop and commercialize at least one Vector from the relevant GSK Development Program as a GSK Product within the projected timelines indicated in the relevant GSK Development Plan for such Program. In the event that TELETHON-HSR reasonably believes that GSK has failed to comply with the obligations of this Section 5.1(c) in any Calendar Year with respect to a particular GSK Development Program or GSK Product under such GSK Development Program, TELETHON-HSR shall have the right to terminate on a Program by Program basis the license granted to GSK for the relevant Collaboration Program or for the ADA-SCID Program, as applicable, depending upon the Program or GSK Product for which GSK has failed to comply with its diligence obligations under this Section 5.1(c), by operation of the applicable provisions of Article 12.

(d) With respect to the ADA-SCID Program and the Collaboration Programs, GSK shall submit to the JSC a detailed summary report on progress made by it since the date of the last report with regard to each GSK Development Vector at least once every [***] during Development and commercialization of such Vector ("the **GSK Development Plan**"). Such GSK Development Plan shall describe, an assessment of (i) the market potential of the GSK Development Vector, (ii) the proposed Clinical Trials (including details of trials proposed and anticipated timelines for the commencement and completion of such trials) and any other studies proposed, regulatory plans, Clinical Trial and commercial supply requirements, and (iii) process development and manufacturing plans with respect to such GSK Development Vector. The GSK Development Plan shall also include an estimated detailed Development timetable up to commercialization of the Product and the identity of the initial development team to be responsible for implementing the GSK Development Plan. The Parties shall meet at least once every [***] to discuss the GSK Development Plan and progress being made by GSK in relation thereto. Within [***] of Regulatory Approval being obtained in relation to a GSK Development Vector GSK shall supply to TELETHON-HSR a summary of GSK's plans for commercialising the GSK Development Vector and shall keep TELETHON-HSR updated in writing once every [***] following the date of Regulatory Approval with regard to progress made in respect of such plans.

5.2 **TELETHON-HSR Development Vectors**

(a) Option Expiration; Collaboration Program Termination. In the event that the Review Period (as may be extended), for an Option with respect to a particular Collaboration Program expires without exercise, or in the event that the JSC or GSK terminates a Collaboration Program, then such Collaboration Program shall become a TELETHON-HSR Development Program, and TELETHON-HSR shall have the exclusive right, at its sole discretion, to Research, Develop and commercialize all Products within such Collaboration Program as TELETHON-HSR Products in the Territory in the Field, alone or with any Third Party or through any Sublicensee, Affiliate or subcontractor. GSK will have no further obligations to make any milestone, royalty or other payments to TELETHON-HSR of any kind under Article 6 with respect to such Products, nor shall GSK have any further obligation to make any milestone, royalty or other payments of any kind to any Third Party on account of any

Third Party license with respect to such Products under any provision of this Agreement. GSK hereby grants, conditional upon the occurrence of such expiration or termination, an exclusive, royalty-free licence under GSK's rights in any Joint IP solely as and to the extent necessary to further develop and commercialize such Products as TELETHON-HSR Products in the Territory in the Field. GSK hereby agrees to negotiate in good faith and under commercially reasonable terms with TELETHON-HSR for an exclusive license under the relevant solely owned GSK IP solely to the extent necessary to further Develop and commercialize such Products as TELETHON-HSR Products in the Territory in the Field.

(b) GSK Development Termination. After exercising an Option with respect to a particular Collaboration Program, GSK may, at its sole discretion and without any penalty or liability (other than the transfer of any data, regulatory filings and other Know-How and grant of rights contemplated under this Section 5.2(b) and to comply with its obligations in Article 12), terminate its Development or commercialization of all the Vectors or GSK Products within such Program upon written notice to TELETHON-HSR. In such event and by operation of the applicable provisions of Article 12, (i) all licenses in and to the Exclusively Licensed IP for such Vectors granted to GSK by TELETHON-HSR shall immediately terminate, (ii) TELETHON-HSR shall have the right to continue Development and commercialization of such Vectors under a TELETHON-HSR Development Program, (iii) the obligations of TELETHON-HSR and rights of GSK under the JSC with respect to such Program will terminate, and (iv) GSK (A) hereby grants, conditional upon the occurrence of such termination, an exclusive, royalty-free licence under GSK's rights in any Joint IP solely as necessary to further Develop and commercialize such Vectors as TELETHON-HSR Products in the Territory in the Field, and GSK hereby agrees to negotiate in good faith and under commercially reasonable terms with TELETHON-HSR for an exclusive license under the relevant solely owned GSK IP solely to the extent necessary to further Develop and commercialize such Products as TELETHON-HSR Products in the Territory in the Field, and (B) GSK shall transfer to TELETHON-HSR, free of charge and within [***] any and all data and Know-How pertaining to

such Vectors (other than any solely owned GSK IP, which will be subject to the negotiation for a license as described above) that are necessary for the continued Development and commercialization of such Vectors in its possession and other related materials, including without limitation copies of all Clinical Trial data and results, and all other Know-How and the like developed by or for the benefit of GSK relating to such Vectors and other documents (other than any solely owned GSK IP, which will be subject to the negotiation for a license as described above) to the extent relating to such Vectors that are necessary or useful in the continued Development and commercialization of such Vectors as TELETHON-HSR Products (including without limitation material documents and agreements relating to the regulatory filings including all Regulatory Approvals and Reimbursement Approvals) throughout the Territory.

5.3 **Safety Data Exchange**

The Parties shall negotiate in good faith a safety data exchange agreement with respect to GSK Products within [***] of GSK's exercise of an Option. The safety data exchange agreement shall facilitate management of safety for all GSK Products covered under such agreement in accordance with standards that are no less stringent than in the ICH guidelines, such that the Parties would be able to comply with all regulatory and legal requirements regarding the management of safety data, by providing for the exchange of relevant information in appropriate format within applicable timeframes.

6 MILESTONES AND ROYALTIES; PAYMENTS

6.1 **Upfront Payment**

GSK, for the exclusive license grant pertaining to the ADA-SCID Program Exclusively Licensed IP and for the exclusive Option rights pertaining to the Collaboration Program Exclusively Licensed IP, and for the non-exclusive license granted in Section 4.3, shall pay to TELETHON-HSR a non-refundable, non-creditable payment of Ten (10) million Euros (€10,000,000) within [***] after receipt of an invoice by GSK on or after the Effective Date. F. Telethon and F. San Raffaele will each receive half of this amount and therefore be entitled to issue, after the Effective Date, separate invoices (to be paid within [***] after receipt of Invoice) for the amount of Five (5) Million Euros each.

6.2 **Development, Regulatory and Commercial Milestones**

(a) Subject to the provisions of this Section 6.2, or after the exercise of the option, GSK shall make the non-refundable, non-creditable milestone payments to TELETHON-HSR that are set forth in the table below on a TELETHON-HSR Collaboration Program-by-TELETHON-HSR Collaboration Program basis or a GSK Development Program-by-GSK Development Program basis, as the case may be, after receipt of an invoice following achievement of the corresponding milestone event with respect to Vectors and GSK Products resulting from the relevant TELETHON-HSR Collaboration Program or GSK Development Program, as the case may be. GSK shall correspond to TELETHON-HSR the payments due for the achievement of milestone events prior to PoC in exchange for the Know-How and Patent Rights generated by TELETHON-HSR upon the achievement of the corresponding specific milestone event as listed in Section 6.2(b). All of the milestones in Section 6.2 shall be payable only once for the relevant Collaboration Program. For clarity, it is understood and agreed that the Clinical PoC Option Exercise Payment shall only be paid if GSK elects to exercise its Option with respect to such Collaboration Program. In the event that GSK, after exercise of its Option, sublicenses its rights to an Affiliate or to a Third Party Sublicensee, GSK shall remain liable to TELETHON-HSR to make all payments owed under this Section 6.2 to TELETHON-HSR on behalf of any such Third Party Sublicensee or Affiliate.

(b) With regard to the Additional Programs, TELETHON-HSR shall communicate to the JSC any potential Additional Program, providing all technical and scientific information necessary for evaluation by the JSC. The JSC shall, within [***] from receipt of TELETHON-HSR's proposal, communicate the decision on whether to approve the Additional Program, for which GSK shall have the final say. If the Additional Program is approved, GSK shall pay [***] to TELETHON-HSR if [***] has been achieved. Otherwise, such payment will be

delayed and made when [***] is achieved. In addition to this payment, GSK shall pay the same milestones for each of the Additional Programs as shown for [***] in the following table, unless the JSC mutually agree that the relevant Additional Program is not comparable to [***] based on criteria such as [***]. In such case, the [***] milestones shown in the following table will be applicable instead, except that no Bonus milestone payments will be payable by GSK.

	M€						
Upfront Payment (all cash)	**10**						
	Programs						
Milestone Events	**Retrovirus ADA-SCID**	**Lentivirus WAS**	**Lentivirus MLD**	**Lentivirus ß Thalass**	**Lentivirus MPS**	**Lentivirus GLD**	**Lentivirus CGD**
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]

* [***].

^ [***].

^^ [***].

*** Confidential Treatment Requested ***

Key Definitions Related to the Milestone Payment Table above:

1. **Program Definitions:**

   a. Retrovirus ADA-SCID = adenosine deaminase-severe combined immunodeficiency gene therapy utilizing a retrovirus vector.

   b. Lentivirus WAS = Wiskott-Aldrich Syndrome gene therapy utilizing a lentivirus vector

   c. Lentivirus CGD = Chronic granulomatous Disease gene therapy utilizing a lentivirus vector

   d. Lentiviurs MLD = Metachromatic leukodystrophy gene therapy utilizing a lentivirus vector

   e. Lentivirus GLD = Globoid cell leukodystrophy gene therapy utilizing a lentivirus vector

   f. Lentivirus MPS = Mucopolysaccaridosis Type I (Hurler) gene therapy utilizing a lentivirus vector

   g. Lentivirus B Thalass = Beta-thalassemia gene therapy utilizing a lentivirus vector

2. [***]

3. [***]. This milestone represents one of the efficacy endpoint of the clinical trials (details on modality and timing of analysis are available in the clinical protocols), set here to a higher threshold in order to provide a stringent validation of our lentiviral vector platform of general validity for all the proposed projects in terms of HSC gene transfer efficacy.

4. [***]. This milestone represents one of the safety endpoint of the clinical trials. The total number and time points of analysis will be dependent on the harvest of patient material as specified for the previous milestone, the relevance of each time point for monitoring the repopulation kinetics and the overall cost and feasibility of the study. This milestone will provide a stringent validation of the lentiviral platform of general validity for all the proposed projects in terms of HSC gene transfer safety.

5. [***]

6.3 Royalties

(a) *Patent and Market Exclusivity Royalty*. GSK shall pay to TELETHON-HSR incremental royalties on the Annual Net Sales by GSK and/or its Affiliate or Sublicensee of each GSK Product, on a country-by-country basis, (1) in those countries of the Territory in which the composition of matter, manufacture, or use of such GSK Product(s) is covered by a Valid Claim within the Patent Rights included in the Exclusively Licensed IP or (2) in those countries in the Territory in which such GSK Product has been granted Market Exclusivity

Rights and such Market Exclusivity Rights are in force at the relevant time of sale in the relevant country, either of scenarios (1) or (2) shall qualify for the **"Patent/Market Exclusivity Royalty"**, in the case of scenarios (1) and (2) at one hundred percent (100%) of the royalty rates set forth in the table below. Royalties will be paid by GSK to TELETHON-HSR on a Program-by-Program basis for total annual Net Sales of Licensed Products resulting from a given Program, as follows and for the duration of the applicable Royalty Term as described below:

Worldwide Net Sales	Royalty Rate
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

The royalty rates above are incremental rates that apply only for the respective increment of worldwide Annual Net Sales described in the Annual Net Sales column and, thus, once a total Annual Net Sales figure is achieved for the year, the royalties owed on any lower tier portion of Annual Net Sales are not adjusted up to the higher tier rate. In the event that GSK, after exercise of its Option, sublicenses its rights to an Affiliate or to a Third Party Sublicensee, GSK shall remain liable to TELETHON-HSR to make all payments owed under this Section 6.3 to TELETHON-HSR on behalf of any such Third Party Sublicensee or Affiliate. The Patent/Market Exclusivity Royalty as provided in this Section 6.3(a) shall be adjusted and subject to the terms and conditions as provided in Section 6.3(b) below.

(b) The royalty rates as described in Section 6.3(a) shall be payable for as long as (i) a Valid Claim of a Patent is pending ([***]) or is issued, which covers the composition of matter, manufacture, or use of the Product being sold in the country of sale, or (ii) Market Exclusivity was formally granted and remains enforceable in such country through orphan drug status. Upon the expiration of the period described in the prior sentence, or at any time when the conditions of neither (i) nor (ii) of this paragraph are met, the applicable

royalty rates described in paragraph (a) above shall be reduced by [***], and such reduced royalty rate shall be payable for so long as there is no significant generic or biosimilars competition, but for a period not to extend beyond the date that is [***] after the date of First Commercial Sale of the Product in such country. The "Royalty Term" shall thus be defined on a Product-by-Product and country-by-country basis as for as long as (i) a Valid Claim of a Patent is pending ([***]) or is issued, which covers the making, use or sale of the Product being sold in the country of sale, (ii) ten (10) years after the First Commercial Sale of the relevant Product in the relevant country or (iii) Market Exclusivity was formally granted and remains enforceable in such country through orphan drug status; whichever of (i), (ii) or (iii), as applicable, is longer. Notwithstanding the above, in the event that significant generic or biosimilars competition achieves a threshold percentage of [***] of market share, there will [***] by GSK.

(c) *Exchange Rates*. For the purposes of determining royalties due Net Sales shall be converted into Pounds Sterling (a) by GSK using average exchange rates calculated and utilized by GSK's group reporting system and published accounts.

(d) *Sublicensing Income*. GSK shall pay to TELETHON-HSR a share of any sublicensing income that it receives from a Third Party beyond the amounts that are owed to TELETHON-HSR hereunder at the rate of [***], including any up-front payment and [***] under article 6.2.

6.4 GSK's Right to Offset Third Party License Costs

(a) TELETHON-HSR and GSK shall each take reasonable measures and cooperate to ensure that any license to be obtained from a Third Party that is necessary for the furtherance of a Program or for the Development, manufacture or commercialization of any Products resulting from a Program shall be sublicenseable to the other if necessary for the exercise of such other Party's rights under this Agreement. If any license costs, milestone payments, royalties, or fees are involved, the Parties shall discuss in advance via the Joint Patent Subcommittee the potential costs and fees for any such

necessary Third Party licenses. GSK shall be entitled to offset [***] any and all costs and payments ([***]) associated with any license required from such Third Party in order for GSK or its Affiliate or Sublicensee to Develop, manufacture and/or commercialize any Product resulting from any Program; provided, however, that TELETHON-HSR shall have the right to reasonably monitor or review the determination by GSK of such offset amounts and that such offset amounts shall be calculated in good faith by GSK, and that such right to offset shall apply only when a Third Party license is used for enabling the Development or commercialization of a Vector or Product, [***].

6.5 Reports; Milestone Payments

GSK shall make all milestone payments within [***] after receipt by GSK of an invoice from TELETHON-HSR with respect to the achievement of such milestone event after GSK has notified TELETHON-HSR or TELETHON-HSR has notified GSK of achievement of the milestone event in accordance with the terms of this Section 6.5. Upon exercise of an Option by GSK, GSK shall pay the applicable Option Exercise Fee within [***] of receipt of an invoice from TELETHON-HSR after notice from GSK of Option exercise pursuant to Section 4.2(c). TELETHON-HSR shall notify GSK in writing promptly, but in no event later than [***], after each achievement of a milestone in Section 6.2. GSK shall notify TELETHON-HSR in writing promptly, but in no event later than [***], after the achievement of any milestone in Section 6.2. GSK shall pay all milestone payments due within [***] after receipt of an invoice for such payment from TELETHON-HSR following the achievement of the corresponding milestone event. All invoices relevant to milestones achievement will be issued separately from F. Telethon and F. San Raffaele with reference to the 50% share of the milestone amount that is owed to each.

6.6 Reports; Royalty Payments

Until the expiration of a GSK's royalty obligations under this Article 6, GSK agrees to make written reports to the other Party within [***] after the end of each [***] covering all sales of Products in the Territory by such Party and its Affiliates and Sublicensees for which invoices were sent during such [***], as well as, in the case of GSK, the amount of Sublicense Income received in such [***], each such written report in

reasonable detail as available to such Party stating for the period in question: (a) the total Net Sales for each Product, (b) a calculation of the royalty payment due on such Net Sales pursuant to Article 6.3 or 6.5, as the case may be. The information contained in each report under this Section 6.6 shall be considered Confidential Information of the reporting Party. Concurrent with the delivery of each such report, each Party shall make the applicable royalty payment due to the other Party under this Article 6 for the [***] covered by such report. With respect to royalties owed hereunder by GSK to TELETHON-HSR, F. Telethon and F. San Raffaele shall each provide GSK with an invoice for their share of such royalties owed by GSK. In the case of transfers or sales of any Product between the royalty-paying Party and an Affiliate or Sublicensee of such Party, a royalty shall be payable only with respect to the sale of such Product to an independent Third Party and not an Affiliate or Sublicensee of the seller.

6.7 Methods of Payments

All payments due from one Party (the "**Payor**") to the other Party (the "**Payee**") under this Agreement shall be paid in Euro by wire transfer to a bank designated in writing by the Payee.

6.8 Accounting

Payor agrees to keep full, clear and accurate records for a maximum period of [***] after the relevant payment is owed pursuant to this Agreement, setting forth the sales and other disposition of Product sold or otherwise disposed of in sufficient detail to enable royalties and compensation payable to the Payee hereunder to be determined. Payor further agrees, upon not less than [***] prior written notice, to permit the books and records to be examined by an independent accounting firm selected by Payee and reasonably acceptable to Payor for the purpose of verifying reports provided by Payor under Section 6.7. Such audit shall not be performed more frequently than once in every period of [***] and shall be conducted under appropriate confidentiality provisions, for the sole purpose of verifying the accuracy and completeness of all financial, accounting and numerical information and calculations provided under this Agreement. Such examination is to be made at the expense of Payee, except in the event that the results of the audit reveal an underpayment of royalties, milestones, or

other payments to Payee under this Agreement of [***] or more per annum over the period being audited, in which case reasonable audit fees for such examination shall be paid by Payor. When calculating Net Sales, the amount of such sales in foreign currencies shall be converted into pounds sterling in accordance with Section 6.3(c).

6.9 Taxes

(a) For VAT, all amounts in this contract are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of TELETHON-HSR on account of any royalties or other payments payable to TELETHON-HSR under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to TELETHON-HSR proof of any such taxes withheld and paid by GSK for the benefit of TELETHON-HSR, and shall, at TELETHON-HSR's request, provide reasonable assistance to TELETHON-HSR in recovering such taxes.

(b) TELETHON-HSR hereby represents and warrants that TELETHON-HSR is resident for tax purposes in Italy and that TELETHON-HSR is entitled to relief from United Kingdom income tax under the terms of the double tax agreement between the UK and Italy. TELETHON-HSR shall notify GSK immediately in writing in the event that TELETHON-HSR ceases to be entitled to such relief.

(c) Pending receipt of formal certification from the UK Inland Revenue, GSK may pay royalty income and any other payments under this Agreement to TELETHON-HSR by deducting tax at a rate specified in the double tax treaty between the UK and Italy. TELETHON-HSR agrees to indemnify and hold harmless GSK against any loss, damage, expense or liability arising in any way from a breach of the above warranties or any future claim by a UK tax authority or other similar body alleging that GSK was not entitled to deduct withholding tax on such payments at source at the treaty rate.

(d) GSK hereby represents and warrants that GSK is resident for tax purposes in the United Kingdom and that GSK is entitled to relief from Italian income tax under the terms of the double tax agreement between Italy and UK. GSK shall notify TELETHON-HSR immediately in writing in the event that GSK ceases to be entitled to such relief.

6.10 Late Payments

Any undisputed amount owed by one Party to the other Party under this Agreement that is not paid within the applicable time period set forth herein shall accrue interest at the rate of [***], or, if lower, the highest rate permitted under applicable law. Where the late payment is caused by the Payee, such as non or late communication of changes to bank details, non response to communications regarding interpretation or dispute of terms etc then no interest will be payable by the Payor.

6.11 Consideration.

The Parties acknowledge that the payments received by TELETHON-HSR hereunder are in consideration for (i) the licenses and Options granted to GSK hereunder with respect to the Exclusively Licensed IP, including TELETHON-HSR Patent Rights, TELETHON-HSR Know-How, TELETHON-HSR's interest in Joint Patent Rights and Joint Know-How (ii) data packages, clinical trial results, regulatory filings and Orphan Drug designations and (iii) TELETHON-HSR's achievement of milestone events.

7 EXCLUSIVITY

7.1 TELETHON-HSR hereby agrees and covenants to work exclusively with GSK on the Programs, and not to grant any license to any Third Party in relation to any of the Programs, until the time that GSK has exercised or declined its last remaining Option right to a Program under the alliance, subject to the provisions of this paragraph below. Prior to working with any Third Party within the Alliance Scope, GSK shall first discuss with TELETHON-HSR at the Joint Steering Committee and shall consider in good faith TELETHON-HSR's views regarding such a Third Party arrangement by GSK, but GSK

shall have the final say on the matter. GSK and TELETHON-HSR shall agree in advance as to the nature of involvement and as to the financial and IP and license terms that would apply to the involvement of any Third Party as a collaborator in any aspects of any of the Programs. TELETHON-HSR agrees that for each Program, for so long as any research, development, or commercial activities are being conducted either by TELETHON-HSR under such Program, or by GSK or its Affiliate or sublicensee pursuant to the exercise of its Option right to such Program, TELETHON-HSR will work exclusively with GSK with respect to the Indication being pursued under such Program for *ex vivo* hematopoietic stem cell gene therapy approaches for monogenic diseases, disorders or conditions, and will not grant any license to any Third Party in relation to such Indication. This provision does not apply to funding or research collaboration agreements that were established by TELETHON-HSR on or related to the Programs prior to the Effective Date. TELETHON-HSR will be permitted under this Section 7.1 to conduct studies using biological material derived from treated patients enrolled in Clinical Studies within the Collaboration Programs with the purpose of further investigating disease targets, disease mechanisms, efficacy, and therapeutic endpoints or readouts of the human clinical trials conducted by TELETHON-HSR under the Collaboration Programs, provided that these studies are permissible under the relevant policies of both GSK and of TELETHON-HSR, are consistent with the express scope of the informed consents obtained from patients, and are permitted under all applicable laws and regulations, and, if any such studies are conducted beyond the Option Point, are mutually approved in advance by the JSC, such approval not to be unreasonably withheld. TELETHON-HSR shall present such proposal for use of such biological samples in writing to the JSC in advance for review and such proposals shall not include any pre-clinical or basic research and shall be only for non-commercial and non-commercially sponsored research and academic purposes, with the purpose being to use the samples and the resulting analysis to advance a Clinical Study that was conducted by TELETHON-HSR under a Collaboration Program hereunder. TELETHON-HSR shall promptly share the results and data obtained from such analysis of biological materials derived from patients with GSK, and GSK shall have the right to use such data and results for the progression of the Programs hereunder after the exercise of its Option. Moreover,(at least until GSK exercises an Option to the relevant Collaboration Program) TELETHON-HSR is entitled to seek to establish, after consultation with GSK at the Joint Steering Committee (but TELETHON-HSR will have final say on the matter), scientific

collaboration and material transfer agreements with other non-commercial research or non-commercial clinical Institutions worldwide on research and clinical activities related to the Program and to seek to obtain, after consultation with GSK at the Joint Steering Committee, (but TELETHON-HSR will have final say on the matter), additional funding from non-commercial entities for activities related to the Programs, provided that these other agreements do not infringe the option terms or reduce or interfere with the scope of the licenses to the Programs to be granted to GSK upon exercise of its Option right.

7.2 Notwithstanding the above provisions of Section 7.1, to the extent not precluded by the express terms of a written agreement existing between TELETHON-HSR and a Third Party as of the Effective Date, prior to initiating any activities or collaboration within the Alliance Scope with any non-commercial or commercial Third Party that might constitute a significant component of an ongoing Program under the alliance or might constitute an Additional Program as described in paragraph 2(g) under the section on "Scope" above, TELETHON-HSR shall first consult with GSK and offer to collaborate with GSK on such potential program as an Additional Program under this alliance, or as a component of an ongoing Program; provided, however, that TELETHON-HSR will have final say on the matter for any potential collaboration with a non-commercial Third Party within the Alliance Scope. GSK will provide written feedback to TELETHON-HSR regarding the proposed subject of potential collaboration within [***] of the date that TELETHON-HSR first offers to collaborate with GSK with regards to such proposed subject matter.

8 INTELLECTUAL PROPERTY

8.1 Ownership

(a) TELETHON-HSR shall own, Control and retain all of its rights, title and interest in and to the TELETHON-HSR IP except to the extent that any rights or licenses are expressly granted to GSK under this Agreement.

(b) GSK shall own, Control and retain all of its rights, title and interest in and to the GSK IP, except to the extent that any rights or licenses are expressly granted to TELETHON-HSR under this Agreement.

(c) TELETHON-HSR and GSK shall jointly own and Control, in equal undivided shares, all Joint IP.

(d) Inventorship for all inventions, and the law governing the rights of joint inventors in relation to one another for joint intellectual property shall be determined in accordance with the laws of the U.S, subject to the licenses and covenants expressly stated under this Agreement.

8.2 Prosecution and Maintenance of Patent Rights

(a) *TELETHON-HSR Patent Rights*.

(1) Except as stated under paragraphs (2) and (3) of this Section 8.2(a) below, during the Term and thereafter, as between the Parties, TELETHON-HSR shall be responsible for the Prosecution and Maintenance of the TELETHON-HSR Patent Rights. TELETHON-HSR will use Commercially Reasonable Efforts to obtain a reasonable scope of patent protection for Vectors that satisfy the Clinical Candidate Selection Criteria, using counsel of its own choice but reasonably acceptable to GSK. TELETHON-HSR shall keep GSK informed through the JPS as to material developments with respect to the Prosecution and Maintenance of the TELETHON-HSR Patent Rights, including by providing copies of all applications, all substantive office actions and responses thereto, or any other substantive documents that TELETHON-HSR receives from any patent office, including without limitation notice of all interferences, reissues, re-examinations, oppositions, appeals or requests for patent term extensions. The JPS will provide oversight of Prosecution and Maintenance, defense and enforcement of the Patent Rights covering the Collaboration Programs and the jointly undertaken activities of the Research Programs under this Agreement. Notwithstanding the exclusion of the ADA-SCID Program from the JSC, the JPS will also provide oversight of Prosecution and Maintenance, defense and enforcement of the Patent Rights covering the ADA-SCID Program to the same extent and in the same manner such oversight is provided to the other Programs under this Agreement. Input shall be provided and consideration undertaken and concluded by the Parties in a

timely manner so as not to jeopardize the pendency of the application under review or otherwise negatively affect or limit the rights of any Party hereto. GSK shall have the right and reasonable opportunity (at its own expense) to review and make comments and recommendations in relation to the Prosecution and Maintenance and management of the TELETHON-HSR Patent Rights, provided it does so promptly, consistent with any filing or other procedural deadlines, and TELETHON-HSR will consider in good faith the recommendations of GSK. TELETHON-HSR shall act in good faith, with respect to the Prosecution and Maintenance of any TELETHON-HSR Patent Rights. Should the Parties fail to agree on any matter in this Section 8.2(a), TELETHON-HSR shall have the final say on such matter.

(2) *After Option Exercise by GSK or for the ADA-SCID Program*. After the exercise of its Option for a given Collaboration Program, and as of the Effective Date for the ADA-SCID Program, for any TELETHON-HSR Patent Rights which are focused mainly on the relevant Program and/or the Vectors or Products included under such Program, GSK shall be responsible at its own cost for the Prosecution and Maintenance of such TELETHON-HSR Patent Rights. The Parties shall discuss and agree at the JPS on a case-by-case basis which TELETHON-HSR Patent Rights will qualify under this paragraph for control of Prosecution and Maintenance by GSK after Option exercise. TELETHON-HSR shall have the right and reasonable opportunity (at its own expense) to review and make comments and recommendations in relation to the Prosecution and Maintenance and management of any such TELETHON-HSR Patent Rights, provided it does so promptly, consistent with any filing or other procedural deadlines, and GSK will consider in good faith the recommendations of TELETHON-HSR. GSK shall act in good faith, with respect to the Prosecution and Maintenance of any TELETHON-HSR Patent Rights after exercise of the Option. Should the Parties fail to agree at the JPS on any matter in this Section 8.2(a) concerning post-exercise of Option matters or for the ADA-SCID Program, GSK shall have the final say on such matter.

(3) *Filing of Divisional applications for TELETHON-HSR Patent Rights*. In the event that any TELETHON-HSR Patent Rights are not focused mainly on the relevant Program and the Vectors or Products included under such Program, but are nonetheless amenable to the filing of a divisional application to separate out such subject matter focused mainly on the relevant Program and the Vectors or Products included thereunder in a separate patent application, the parties shall consider on a case-by-case basis the filing of such divisional applications and, where appropriate and requested by GSK, shall file such divisional patent applications in the name of TELETHON-HSR. GSK shall be responsible for the Prosecution and Maintenance of such TELETHON-HSR Patent Rights under such divisional patent applications as of the date it exercises its Option to the relevant Program. TELETHON-HSR shall thereafter have the right and reasonable opportunity (at its own expense) to review and make comments and recommendations in relation to the Prosecution and Maintenance and management of such TELETHON-HSR Patent Rights, provided it does so promptly, consistent with any filing or other procedural deadlines, and GSK will consider in good faith the recommendations of TELETHON-HSR. GSK shall act in good faith, with respect to the Prosecution and Maintenance of any TELETHON-HSR Patent Rights after exercise of the option. Should the Parties fail to agree at the JPS on any matter in this Section 8.2(a) concerning post-exercise of Option matters, GSK shall have the final say on such matter.(b) *GSK Patent Rights*. As between the Parties, GSK shall control the Prosecution and Maintenance of the GSK Patent Rights. Notwithstanding the foregoing, GSK shall use Commercially Reasonable Efforts to consult with TELETHON-HSR through the JPS in connection with the Prosecution and Maintenance of the GSK Patent Rights; provided, however, that GSK shall not be required to disclose any confidential information that is not specific to the Programs. Input shall be provided and consideration undertaken and concluded by the Parties in a timely manner so as not to jeopardize the pendency of the application under review or otherwise negatively affect or limit the rights of any Party hereto. TELETHON-HSR shall have the right and reasonable opportunity (at its own expense) to review and make comments and recommendations in relation to the Prosecution and Maintenance and management of the GSK Patent Rights, provided it does so promptly consistent with any filing or procedural deadlines, and GSK will consider in good faith the recommendations of TELETHON-HSR. GSK shall act in good faith, with respect to the Prosecution and Maintenance of any GSK Patent Rights. Should the Parties fail to agree on any matter in this Section 8.2(b), GSK shall have the final say on such matter.

(b) *Joint Patent Rights owned jointly between TELETHON-HSR and GSK*. GSK shall be responsible for the Prosecution and Maintenance of the Joint Patent Rights, regardless of whether such Joint Patent Rights relate to the ADA-SCID Program, a Collaboration Program, or the jointly undertaken activities of one of the Research Programs. GSK will use Commercially Reasonable Efforts to obtain a reasonable scope of patent protection for Vectors that satisfy the Clinical Candidate Selection Criteria covered by claims of such Joint Patent Rights, using counsel, including in-house patent counsel, of its own choice but reasonably acceptable to TELETHON-HSR. GSK shall keep TELETHON-HSR informed through the JPS as to material developments with respect to the Prosecution and Maintenance of such Joint Patent Rights, including by providing copies of all applications and all substantive office actions and responses thereto, or any other substantive documents that GSK receives from any patent office, including without limitation notice of all interferences, reissues, re-examinations, oppositions, appeals or requests for patent term extensions. Input shall be provided and consideration undertaken and concluded by the Parties in a timely manner so as not to jeopardize the pendency of the application under review or otherwise negatively affect or limit the rights of any Party hereto. TELETHON-HSR shall have the right and reasonable opportunity (at its own expense) to review and make comments and recommendations in relation to the Prosecution and Maintenance and management of the Joint Patent Rights, provided it does so promptly, consistent with any filing deadlines, and GSK will consider in good faith the recommendations of TELETHON-HSR. GSK shall act in good faith with respect to the Prosecution and Maintenance of any Joint Patent Rights. Any dispute regarding the Prosecution and Maintenance of any Joint Patent Rights shall be resolved in accordance with Section 3.2(g).

(c) *Filing Decision or Prosecution Lapse*. If, during the Term, the Party responsible for Prosecuting and Maintaining the TELETHON-HSR Patent Rights, GSK Patent Rights or Joint Patent Rights, as the case may be, in any country, decides not to file such Patent Rights or intends to allow such Patent Rights

to lapse or become abandoned without having first filed a substitute, the Party Prosecuting or Maintaining such Patent Rights shall notify the other Party of such decision or intention at least sixty (60) Calendar Days prior to the date upon which the subject matter of such Patent Rights shall become unpatentable or such Patent Rights shall lapse or become abandoned. The other Party shall thereupon have the right, but not the obligation, to assume responsibility for the Prosecution and Maintenance of such Patent Rights at its own expense with counsel of its own choice.

(d) *Cooperation Regarding the Filing and Prosecution of Divisional Patent Applications*. At either Party's request, the Parties shall discuss and consider the appropriateness of filing a divisional patent application at the JPS and cooperate with one another in good faith to file and prosecute divisional Patent applications with respect to the TELETHON-HSR Rights and the Joint Patent Rights for which either Party is responsible for Prosecution and Maintenance pursuant to this Section 8.2 if practicable and if necessary or desirable to divide subject matter relating to one or more Programs from other subject matter that is not subject to this Agreement to facilitate the control by the respective Parties of the Prosecution and Maintenance of Patents as allocated in accordance with this Article 8.

8.3 Patent Costs

(a) *TELETHON-HSR Patent Rights and GSK Patent Rig*hts. TELETHON-HSR shall be responsible for all Patent Costs incurred with respect to any TELETHON-HSR Patent Rights. GSK shall be responsible for all Patent Costs incurred by GSK with respect to GSK Patent Rights, unless and until such time as GSK acquires control of Prosecution and Maintenance of such TELETHON-HSR Patents in accordance with the provisions of Section 8.2, at which time GSK shall be responsible for the subsequent costs of Prosecution and Maintenance of such TELETHON-HSR Patent Rights.

(b) *Joint Patent Rights owned jointly by TELETHON-HSR and GSK*. GSK shall be responsible for all Patent Costs incurred by GSK with respect to the Prosecution and Maintenance of Joint Patent Rights owned jointly by

TELETHON-HSR and GSK, unless and until such time as TELETHON-HSR acquires control of Prosecution and Maintenance for any such Joint Patents, or by the filing of any divisional patent application in accordance with the provisions of Section 8.2, at which time TELETHON-HSR shall be responsible for the subsequent costs of Prosecution and Maintenance of any such Joint Patent Rights.

(c) *TELETHON-HSR Patent Rights.* Up to the Option Point, GSK will provide reimbursement of patent costs related to GSK's coverage requirements for Prosecution and Maintenance in countries requested by GSK which exceed those already planned by TELETHON-HSR, which usually include the following countries: US, EP, CA, JP, AU.

8.4 Defense of Infringement Claims Brought by Third Parties.

(a) *Infringement Claims by Third Parties*. In the event that a Third Party asserts that the manufacture, use, sale, offer for sale or importation of any Vector or Product infringes a Patent Right of such Third Party, then the Party receiving notice of such action shall promptly notify the other Party and the following shall apply:

(b) *Vectors in a TELETHON-HSR Development Program or Collaboration Program*. If a Third Party asserts that the manufacture, use, sale, offer for sale or importation of any Vector in a Collaboration Program or any Vector within a TELETHON-HSR Development Program infringes a Patent Right of such Third Party, then, subject to Section 8.4(d) below, TELETHON-HSR shall have the primary right but not the obligation to defend against any such assertions at its cost and expense. In the event TELETHON-HSR elects to defend against any such Third Party claims, TELETHON-HSR shall have the sole right to direct the defense of any such Third Party claims and to elect to settle such claims, but only with the prior written consent of GSK for a proposed settlement in circumstances where GSK has not exercised its Option in relation to that Collaboration Program, such consent not to be unreasonably withheld or delayed. In the event that TELETHON-HSR elects not to defend against such Third Party claims within [***] of learning of same, GSK shall have the right,

subject to Section 8.4(d) below, but not the duty, to defend against such action in circumstances where GSK has not exercised its Option in relation to that Collaboration Program and thereafter shall have the sole right to direct the defense of any such Third Party claim(s), including the right to settle such claims, but only with the prior written consent of TELETHON-HSR for a proposed settlement, such consent not to be unreasonably withheld or delayed. Nevertheless, with regard to any actions taken by Third Parties directly against GSK, GSK shall have the primary right but not the obligation to defend itself against any such Third Party actions at its cost and expense. In the event GSK elects to defend against any such Third Party claims, GSK shall have the sole right to direct the defense of any such Third Party claims and to elect to settle such Third Party claims. In any event, the Parties shall reasonably assist one another and cooperate in any such litigation at the other's request without expense to the requesting Party. Each Party may, at its own expense, and with its own counsel join any defense brought by the other Party.

(c) *GSK Development Vectors*. If a Third Party asserts that the manufacture, use, sale, offer for sale or importation of any GSK Development Vector or GSK Product infringes a Patent Right of such Third Party, then, subject to Section 8.4(d) below, GSK shall have the primary right but not the obligation to defend against any such assertions at its cost and expense. In the event GSK elects to defend against any such Third Party claims, GSK shall have the sole right to direct the defense of such Third Party claims and to elect to settle such claims. In the event that GSK elects not to defend against such Third Party claims within [***] of learning of same, TELETHON-HSR shall have the right, subject to Section 8.4(d) below, but not the duty, to defend against such an action and thereafter shall have the sole right to direct the defense of any such Third Party claim(s), including the right to settle such claims. In any event, the Parties shall reasonably assist one another and cooperate in any such litigation at the other's request without expense to the requesting Party. Each Party may at its own expense and with its own counsel join any defense brought by the other Party.

(d) *Indemnification Provisions.* Notwithstanding the foregoing, in the event that any Third Party claim is brought against a Party as set forth above, and such claim is subject to indemnification obligations as set forth in Article 11, then the Indemnification provisions shall control with respect to which Party undertakes the defense of such Third Party claim.

8.5 Enforcement of TELETHON-HSR or GSK Patent Rights.

(a) *Duty to Notify of Infringement*. If either Party learns of an infringement, unauthorized use, misappropriation or threatened infringement by a Third Party, or that any Third Party has filed a declaratory judgment action against either Party alleging non-infringement of any Patent Rights with respect to any Joint Patent Rights, TELETHON-HSR Patent Rights, or GSK Patent Rights ("**Competitive Infringement**"), such Party shall promptly notify the other Party, and shall reasonably endeavour to do so, within [***] of becoming aware of such infringement and shall provide such other Party with available evidence of such Competitive Infringement.

(b) *Prior to Exercise of Option*. Prior to GSK's exercise of an Option, with respect to any Joint Rights or any TELETHON-HSR Patent Rights that is the subject of such Competitive Infringement, TELETHON-HSR shall have the primary right to bring and control any such action. Unless subject to an agreement between TELETHON-HSR and a Third Party in existence as of the Effective Date that would preclude TELETHON-HSR from granting such right to GSK, if TELETHON-HSR fails to bring any such action or proceeding within a period of [***] after first being notified of such Competitive Infringement (or in the case of a declaratory judgment action, within [***] after receiving notice of such declaratory judgment action, to prevent or abate any actual or alleged infringement or defend such declaratory judgment) ("Competitive Infringement Action Period"), then GSK shall have the right, but not the obligation, to bring and control any such action by counsel of its own choice, and TELETHON-HSR shall have the right to be represented in any such action by counsel of its own choice at its own expense. If GSK fails to bring an action or proceeding with respect to such Competitive Infringement within a period of [***] after the expiration of the Competitive Infringement Action Period, then TELETHON-HSR shall have the on-going right to pursue such action.

(c) *Following Exercise of Option*. Following GSK's exercise of an Option, and before GSK's termination of Development and commercialization, with respect to the Program containing Vectors that are the subject of any Competitive Infringement, GSK shall have the primary right, but not the obligation, to institute, prosecute, and control any action or proceeding with respect thereto (including any action or proceeding with respect to any Joint Patent Rights or TELETHON-HSR Patent Rights) by counsel of its own choice, and TELETHON-HSR shall have the right, at its own expense, to be represented in that action by counsel of its own choice. If GSK fails to bring an action or proceeding within a period of [***] after first being notified of such Competitive Infringement, TELETHON-HSR shall have the right to bring and control any such action by counsel of its own choice, and GSK shall have the right to be represented in any such action by counsel of its own choice at its own expense. TELETHON-HSR shall, at GSK's cost, cooperate and provide assistance to GSK towards lending their name to proceed against infringement, subject to GSK indemnifying F. Telethon and F. San Raffaele under the terms and conditions of Sections 11.1, 11.3, 11.4 and 11.6 in respect of any direct costs, losses or liabilities owed to a Third Party as a result of taking such actions and being a party to such proceedings, except to the extent that such costs, losses or liabilities arise out of or result from or are attributable to the negligence, recklessness or wrongful intentional acts or omissions of F. Telethon and/or F. San Raffaele and/or its Affiliates and/Sublicensees, or their respective directors, officers, employees or agents

(d) *After GSK's Termination of a Program*. After GSK's termination of Development and commercialization with respect to a Program containing Vectors or Products that are the subject of any Competitive Infringement of the TELETHON-HSR Patent Right or Joint Patent Rights, TELETHON-HSR shall have the primary right, but not the obligation, to institute, prosecute, and control any action or proceeding with respect thereto by counsel of its own choice. Notwithstanding the foregoing, to the extent that (a) such Competitive Infringement occurred prior to the termination of the applicable Program and (b) TELETHON-HSR fails to bring any such action or proceeding within a period of [***] after first being notified of such Competitive

Infringement, then GSK shall have the right, but not the obligation, to bring and control any such action by counsel of its own choice at its own expense, and TELETHON-HSR shall have the right to be represented in any such action by counsel of its own choice at its own expense.

(e) *Settlement*. A settlement or consent judgment or other voluntary final disposition of a suit under this Article 8 may not be entered into without the prior written consent of the Party not bringing the suit, such consent not to be unreasonably withheld or delayed; provided that such settlement, consent judgment or other disposition does not admit the invalidity or unenforceability of the relevant Patent Rights in the TELETHON-HSR Patent Rights, GSK Patent Rights, or Joint Patent Rights, and provided further, that any rights granted under the relevant Patent Rights to continue the infringing activity in such settlement, consent judgment or other disposition shall be limited to those rights that the granting Party otherwise has the right to grant, and provided further, that any settlement, consent judgment or other disposition shall not include the grant of any license, covenant or other rights to any Third Party that would limit or interfere with or reduce the scope of the subject matter included under the exclusive licenses to be granted to GSK pursuant to the exercise of any of its Options to Programs under Section 4.2(b), and further provided that such settlement does not impose any obligation on, or otherwise adversely affect the other Party.

(f) *Share of Recoveries*. If one Party brings any such action or proceeding in accordance with this Section 8.5, the other Party agrees to be joined as a Party plaintiff where necessary and to give the first Party reasonable assistance (at the expense of the Party bringing suit) and authority to file and prosecute the suit. Any damages or other monetary awards recovered shall be shared as follows: (i) the amount of such recovery actually received by the Party controlling such action shall first be applied to the out-of-pocket costs of such action; and then (ii) any remaining proceeds shall be allocated between the Parties such that the Party bringing suit under this Section 8.5 retains [***].

(g) *35 USC 271(e)(2) Infringement*. Notwithstanding anything to the contrary in this Section 8.5, for infringement under 35 USC 271(e)(2) where GSK has exercised its Option or for the ADA-SCID Program and where GSK is the holder of the applicable NDA, and for so long as GSK maintains or retains its exclusive license under such Option, GSK shall have the sole right to initiate legal action to enforce all GSK Patent Rights and TELETHON-HSR Patent Rights licensed to it against infringement or misappropriation by Third Parties or defend any declaratory judgment action relating thereto at its sole expense. Any such suit may be in the name of GSK or jointly with TELETHON-HSR as required by law, subject to GSK indemnifying F. Telethon and F. San Raffaele under the terms and conditions of Sections 11.1, 11.3, 11.4 and 11.6 in respect of any direct costs, losses or liabilities owed to a Third Party as a result of taking such actions and being a party to such proceedings, except to the extent that such costs, losses or liabilities arise out of or result from or are attributable to the negligence, recklessness or wrongful intentional acts or omissions of F. Telethon and/or F. San Raffaele and/or its Affiliates and/Sublicensees, or their respective directors, officers, employees or agents.

(h) *Patent Listing*. GSK shall be responsible for performing all patent listing acts and requirements for the Product with respect to which GSK has the exclusive rights pursuant to exclusive licenses granted under Article 4 to Develop and commercialize, and that have become the subject of a Marketing Authorisation Application submitted to any applicable Regulatory Authority. Such acts and requirements include all so-called “Orange Book” listings required under the US Hatch-Waxman Act, all so-called “Patent Register” listings as required in Canada, all acts required of the reference product sponsor under the US Biologicals Price Competition and Innovation Act of 2009 (42 U.S.C. § 262) (“Biologics Act”), or any foreign equivalents thereof. Specifically, GSK will control all of the actions, filings, and communications with any follow-on biologic applicant under the Biologics Act, including generating the following documents: (i) the list of patents that GSK believes could be reasonably asserted to be infringed by the launch of the biosimilars product; (ii) the list of patents, if any, which GSK would be willing to license to the follow-on biologic applicant; (iii) the detailed statement describing the

factual and legal basis for why each listed patent will be infringed by the follow-on biologic applicant; and (iv) the response to the follow-on biologic applicant's statement regarding validity and enforceability of each of the listed patents. Prior to such listings, the Parties will meet, through the JPS, to evaluate and identify all applicable Patents, and GSK shall have the right to review, where reasonable, original records relating to any invention for which Patents are being considered by the JPS for any such listing. Notwithstanding the preceding sentence, GSK will retain final decision-making authority as to the listing of all applicable Patents for the Product and all other acts pertaining to such patent listings as required by law, statue or regulation, regardless of which Party owns such Patent, and any such final decision made in good-faith on the matter shall not be subject to any further review under Section 3.2(d) or otherwise under this Agreement. For the avoidance of doubt, any decision made by GSK under this Section 8.5 shall not be used to determine, as between the Parties, whether a Patent contains any Valid Claim or whether any Product is covered by any Valid Claim.

9 CONFIDENTIALITY

9.1 Confidentiality; Exceptions

Except to the extent expressly authorized by this Agreement or otherwise agreed in writing, the Parties agree that the receiving Party (the "**Receiving Party**") shall keep confidential and shall not publish or otherwise disclose or use for any purpose other than as provided for in this Agreement any Know-How or other confidential and proprietary information and materials, patentable or otherwise, in any form (written, oral, photographic, electronic, magnetic, or otherwise) which is disclosed to it by the other Party (the "**Disclosing Party**") or otherwise received or accessed by a Receiving Party in the course of performing its obligations or exercising its rights under this Agreement, including but not limited to trade secrets, know-how, inventions or discoveries, proprietary information, formulae, processes, techniques and information relating to a Party's past, present and future marketing, financial, and Research and Development activities of any product or potential product or useful technology of the Disclosing Party and the pricing thereof (collectively, "**Confidential Information**"), except to the extent that it can be established by the Receiving Party that such Confidential Information:

(a) was in the lawful knowledge and possession of the Receiving Party prior to the time it was disclosed to, or learned by, the Receiving Party, or was otherwise developed independently by the Receiving Party, as evidenced by written records kept in the ordinary course of business, or other documentary proof of actual use by the Receiving Party;

(b) was generally available to the public or otherwise part of the public domain at the time of its disclosure to the Receiving Party;

(c) became generally available to the public or otherwise part of the public domain after its disclosure and other than through any act or omission of the Receiving Party in breach of this Agreement; or

(d) was disclosed to the Receiving Party, other than under an obligation of confidentiality, by a Third Party who had no obligation to the Disclosing Party not to disclose such information to others.

9.2 **Authorized Disclosure.** Except as expressly provided otherwise in this Agreement, a Receiving Party may use and disclose Confidential Information of the Disclosing Party as follows: (i) under appropriate confidentiality provisions similar to those in this Agreement, in connection with the performance of its obligations or exercise of rights granted or reserved in this Agreement (including the rights to commercialize Products and to grant licenses and sublicenses hereunder); or (ii) to the extent such disclosure is reasonably necessary in filing or prosecuting patent, copyright and trademark applications, prosecuting or defending litigation, complying with applicable governmental regulations, obtaining regulatory approval, conducting pre-clinical activities or Clinical Trials, marketing Products, or otherwise required by law; *provided, however*, that if a Receiving Party is required by law or regulation to make any such disclosure of a Disclosing Party's Confidential Information it will, except where impracticable for necessary disclosures, for example in the event of medical emergency, give reasonable advance notice to the Disclosing Party of such disclosure requirement and, except to the extent inappropriate in the case of patent

applications, will use its reasonable efforts to secure confidential treatment of such Confidential Information required to be disclosed; or (iii) in communication with investors, consultants, advisors or others on a need to know basis, in each case under appropriate confidentiality provisions substantially equivalent to those of this Agreement; or (iv) to the extent mutually agreed to in writing by the Parties; provided, however, that, in each of the above situations, the Receiving Party shall remain responsible for any failure by any Person who receives the Confidential Information pursuant to this Section 9.2 to treat such Confidential Information as required under this Article 9.

9.3 **Press Release; Disclosure of Agreement.** On or promptly after the Effective Date, the Parties shall jointly issue a public announcement of the execution of this Agreement. Neither Party shall be free to issue any press release or other public disclosure regarding the Agreement or the Parties' activities hereunder, or any results or data arising hereunder, except (a) with the other Party's prior written consent, or (b) for any disclosure that is reasonably necessary to comply with applicable national securities exchange listing requirements or laws, rules or regulations, with the other Party's consent not to be unreasonably withheld or delayed beyond a time reasonably in advance of the required disclosure deadline necessary to comply with applicable national securities exchange listing requirements or laws, rules or regulations. The Parties agree to consult with each other reasonably and in good faith with respect to the text and timing of any such press releases prior to the issuance thereof, and a Party may not unreasonably withhold consent to such releases. Except to the extent required by law or as otherwise permitted in accordance with this Section 9.3, neither Party shall make any public announcements concerning this Agreement or the subject matter hereof without the prior written consent of the other, which shall not be unreasonably withheld or delayed. Each Party agrees to provide to the other Party a copy of any public announcement regarding this Agreement or the subject matter thereof as soon as reasonably practicable under the circumstances prior to its scheduled release. Except under extraordinary circumstances, when the following notice may not be possible but in which event the press release will still be provided to the other Party for comment before release, each Party shall provide the other with an advance copy of any such announcements at least [***] prior to its scheduled release. Each Party shall have the right to expeditiously review and recommend

changes to any such announcement and, except as otherwise required by laws, rules or regulations, the Party whose announcement has been reviewed shall remove any Confidential Information of the reviewing Party that the reviewing Party reasonably deems to be inappropriate for disclosure. The principles to be observed by TELETHON-HSR and GSK in any such permitted public disclosures with respect to this Agreement shall be: accuracy and completeness, the requirements of confidentiality under this Article 9, and the normal business practice in the pharmaceutical and biotechnology industries for disclosures by companies comparable to TELETHON-HSR and GSK. Notwithstanding the foregoing, to the extent information regarding this Agreement under the ADA-SCID Program, or under a Collaboration Program, or under the jointly undertaken activities of a Research Program has already been publicly disclosed in the same context, either Party may subsequently disclose the same information to the public without the consent of the other Party. Each Party shall be permitted to disclose the terms of this Agreement, in each case under appropriate confidentiality provisions substantially equivalent to those of this Agreement, to any actual or potential acquirors, investors, merger partners, and professional advisors.

9.4 **Termination of Prior Agreement.** This Agreement supersedes the Confidentiality Agreement between TELETHON-HSR and GSK dated February 15th, 2010, including any and all amendments thereto. All information exchanged between the Parties under that agreement shall be deemed Confidential Information hereunder and shall be subject to the terms of this Article 9.

9.5 **Publications.** Neither Party nor its Affiliates shall publish or publicly disclose the results of any of the Research and/or Development activities conducted by either Party under this Agreement under the ADA-SCID Program, or under a Collaboration Program, or under the jointly undertaken activities of a Research Program without the prior written mutual consent of the JSC working through the JPS, except as expressly permitted in this Section 9.5 or otherwise in this Agreement. The Parties recognize that it may be useful or required to publish or publicly disclose the results of Research and Development work on Programs, and each Party (and its Affiliates and Sublicensees) shall be free to publish or publicly disclose such results, subject to the prior review by the JSC for patentability and protection of its Confidential Information as described in this Section 9.5. For TELETHON-HSR, the publication right conveyed by the preceding sentence shall apply solely to Vectors or Products prior to the exercise

of an Option by GSK to the relevant Collaboration Program, if approved by JSC, such approval not to be unreasonably withheld or delayed. The Party that desires to publish results hereunder shall provide to the JSC and JPS a copy of such proposed abstract, manuscript, or presentation no less than [***] prior to its intended submission for publication. The JSC shall respond in writing promptly and in no event later than [***] after receipt of the proposed material, with one or more of the following: (i) comments on the proposed material, which the publishing Party must consider in good faith, (ii) a specific statement of concern, based upon the need to seek patent protection, or to block publication if the JSC determines that the proposed disclosure is intellectual property that should be maintained as a trade secret to protect a Vector or Product or any Research and/or Development activities conducted under this Agreement, or (iii) an identification of the other Party's Confidential Information that is contained in the material reviewed. In the event of concern over patent protection or whether maintaining a trade secret would be a priority, the publishing Party agrees not to submit such publication or to make such presentation that contains such information until the JSC through the JPS is given a reasonable period of time (such period of time to be no more than [***]) to seek patent protection for any material in such publication or presentation which it believes is patentable, or to resolve any other issues or to abandon such proposed publication if the JSC reasonably determines in good faith that maintaining such information as a trade secret is a commercially-reasonable priority. Any Confidential Information of such other Party shall be removed. Furthermore, with respect to any proposed abstracts, manuscripts or summaries of presentations by investigators or other Third Parties, such materials shall be subject to review under this Section 9.5 to the extent that GSK or TELETHON-HSR (as the case may be) has the right to do so. For clarity, (a) prior to the exercise of the relevant Option to a given Collaboration Program by GSK, any proposed publication by TELETHON-HSR relating to a Collaboration Program or any Vectors shall be subject to review by the JSC in accordance with the terms of this Section 9.5, but after the expiration of the relevant Option without exercise by GSK or after the termination of a Program which then reverts to TELETHON-HSR, TELETHON-HSR shall then be free to publish or publicly disclose any results that relate to any Vectors or TELETHON-HSR Products in such Collaboration Program or TELETHON-HSR Development Program without any review by the JSC under this Section 9.5, unless such proposed disclosure or publication contains any Joint IP or GSK IP, in which case JSC shall have the right to

review and approve such disclosure as stated under this Section 9.5 above, and (b) after the exercise by GSK of its Option to a Program, except as required by law or securities regulations, TELETHON-HSR shall not have the right to make any publication relating to such Collaboration Program or any Vectors or Products or GSK Development Vectors or GSK Products without the prior written consent of the JSC, which is not to be unreasonably withheld, and GSK shall have the right to make any such publication relating to such Collaboration Program or any Vectors or GSK Development Vectors or Products or GSK Products subject to review by the JSC under this Section 9.5. Such review will not take longer than 15 Calendar Days. Notwithstanding the above, if TELETHON-HSR seeks to publish any publication regarding the ADA-SCID Program, it shall provide GSK with an advance copy of such publication and obtain GSK's prior consent before publication, which is not to be unreasonably withheld. Notwithstanding the foregoing, to the extent information regarding this Agreement under the ADA-SCID Program, or under a Collaboration Program, or under the jointly undertaken activities of a Research Program has already been evaluated by the JPS and JSC and disclosed, TELETHON-HSR will be free to disclose the same information to the public without the consent of the other Party. For the avoidance of doubt, any substantive changes to a proposed disclosure, such as the inclusion of new data or analysis that was not previously approved by the JSC through the JPS, must be submitted to and approved by the JPS prior to its disclosure.

9.6 **Clinical Trial Register.** Each of GSK and TELETHON-HSR shall have the right, to the extent permitted by and in compliance with all applicable laws and regulations, to publish summaries of results from any human Clinical Trials conducted by such Party under this Agreement on its Clinical Trials registry, without requiring the consent of the other Party, subject to the last sentence of this Section 9.6; provided, however, that GSK shall have no right, without the consent of TELETHON-HSR, to so publish data generated by TELETHON-HSR prior to GSK's exercise of its Option with respect to the relevant Vectors under the relevant Collaboration Program, and, after the exercise of its Option to such Collaboration Program, GSK shall have the right to so publish any previously existing and/or any subsequently arising data that is or may be generated by either TELETHON-HSR or GSK or by their respective Affiliates or Sublicensees with respect to the relevant Vector(s) without obtaining the consent of TELETHON-HSR, except with respect to any Vectors which are being pursued under a TELETHON-HSR

Development Program after termination by GSK of such Vectors as GSK Development Vectors or after GSK declines to exercise its Option with respect to such Collaboration Program. In addition, after the exercise of its Option by GSK to a particular Collaboration Program, TELETHON-HSR shall not have the right to publish any of such data, without the prior consent of GSK, pertaining to the relevant Vectors or the Collaboration Program, except with respect to any Vectors which are being pursued under a TELETHON-HSR Development Program after termination by GSK of such Vectors as GSK Development Vectors. The Parties shall discuss and reasonably cooperate in order to facilitate the process to be employed in order to ensure the publication of any such summaries of human Clinical Trials data and results as required on the Clinical Trial registry of each respective Party, and shall provide the other Party via submission to the Joint Patent Subcommittee established under Section 3.2(g), at least [***] prior notice to review the Clinical Trials results to be published for the purposes of preparing any necessary Patent filings.

10 REPRESENTATIONS AND WARRANTIES

10.1 **Representations and Warranties of Both Parties.** Each Party hereby represents and warrants to the other Party, as of the Effective Date, that:

(a) such Party is duly organized, validly existing and in good standing under the laws of the jurisdiction of its incorporation and has full corporate power and authority to enter into this Agreement and to carry out the provisions hereof;

(b) such Party has taken all necessary action on its part to authorize the execution and delivery of this Agreement and the performance of its obligations hereunder;

(c) this Agreement has been duly executed and delivered on behalf of such Party, and constitutes a legal, valid, binding obligation, enforceable against it in accordance with the terms hereof;

(d) the execution, delivery and performance of this Agreement by such Party does not conflict with any agreement or any provision thereof, or any instrument or understanding, oral or written, to which it is a Party or by which it is bound, nor violate any law or regulation of any court, governmental body or administrative or other agency having jurisdiction over such Party;

(e) no government authorization, consent, approval, license, exemption of or filing or registration with any court or governmental department, commission, board, bureau, agency or instrumentality, domestic or foreign, under any applicable laws, rules or regulations currently in effect, is or will be necessary for, or in connection with, the transaction contemplated by this Agreement or any other agreement or instrument executed in connection herewith, or for the performance by it of its obligations under this Agreement and such other agreements; and

(f) it has not employed (and, to the best of its knowledge without further duty of inquiry, has not used a contractor or consultant that has employed) any individual or entity debarred by the FDA (or subject to a similar sanction of EMA), or, to the best of its knowledge without further duty of inquiry, any individual who or entity that is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA), in the conduct of any pre-clinical activities or clinical studies of Vectors.

10.2 **Representations, Warranties and Covenants of TELETHON-HSR.** TELETHON-HSR hereby represents and warrants to GSK, as of the Effective Date, and covenants to GSK during the Term (or the applicable portion thereof) as applicable for Sections 10.2(c) and 10.2.(e) and 10.2 (f), that:

(a) To its knowledge, TELETHON-HSR is the owner of, or has Control via a license to, the TELETHON-HSR IP;

(b) To its knowledge, TELETHON-HSR has the right to grant, and no consent is or will be required from any Third Party in connection with, all rights, licenses and sublicenses it purports to grant to GSK with respect to the TELETHON-HSR IP or TELETHON-HSR's interest in Joint IP under this Agreement;

(c) TELETHON-HSR has not withheld from GSK any material data or any material correspondence, including without limitation any correspondence to or from any Regulatory Authority, in existence as of the Effective Date with respect to the ADA-SCID Program, the Collaboration Programs or Vectors that it is aware would have a material adverse effect upon GSK's scientific, commercial, safety and regulatory assessment of the liabilities of the collaboration between the Parties as contemplated under this Agreement;

(d) To its knowledge, TELETHON-HSR has disclosed or provided access to as of the Effective Date, and thereafter until the exercise or expiration of the Option with respect to a Collaboration Program shall disclose to GSK and exchange, all material data and information and all correspondence to or from any Regulatory Authority then available, regardless of whether such data, correspondence and information would have a positive or negative impact on the potential commercial, scientific or strategic value or attractiveness of the Vectors, that is in TELETHON-HSR's reasonable business judgment material to a reasonable assessment by GSK of the scientific, commercial, safety, and regulatory liabilities of the Vectors to be considered by GSK in deciding whether or not to exercise its Option with respect to such Collaboration Program;

(e) During the Term until the exercise or expiration of an Option, TELETHON-HSR will not grant to any Third Party any right, license or lien in relation to a Collaboration Program or to the ADA-SCID Program that would conflict or interfere with any of the rights or licenses granted or to be granted to GSK hereunder pursuant to the exercise of such Option or by operation of the provisions of Article 12, unless expressly mutually agreed in advance by the Parties in writing; and

(f) F. Telethon and F. San Raffaele shall be jointly and severally liable for all of the obligations of TELETHON-HSR under this Agreement.

10.3 **Mutual Covenants.** Each Party hereby covenants to the other Party that:

(a) All employees of such Party or its Affiliates working under this Agreement will be under the obligation to assign all right, title and interest in and to their inventions and discoveries, whether or not patentable, to such Party as the sole owner thereof;

(b) Such Party will not employ (or, to the best of its knowledge without further duty of inquiry, will not use any contractor or consultant that employs) any individual or entity debarred by the FDA (or subject to a similar sanction of EMA) or, to the best of its knowledge without further duty of inquiry, any individual who or entity that is the subject of an FDA debarment investigation or proceeding (or similar proceeding of EMA), in the conduct of its activities under any Program;

(c) Such Party shall (a) perform its activities pursuant to this Agreement in compliance with good laboratory and clinical practices and cGMP, where appropriate, in each case as applicable under the laws and regulations of the country and the state and local government wherein such activities are conducted; (b) with respect to the care, handling and use in Research and Development activities hereunder of any non-human animals by or on behalf of such Party, at all times comply (and shall ensure compliance by any of its subcontractors) with all applicable federal, state and local laws, regulations and ordinances, and also with the most current best practices for comparable-sized pharmaceutical or biotechnology companies for the proper care, handling and use of animals in pharmaceutical Research and Development activities, and at all times with the "3R Principles" (reducing the number of animals used, replacing animals with non-animal methods whenever possible and refining the Research techniques used), subject to the other Party's reasonable right of inspection; (c) promptly and in good faith undertake reasonable corrective steps and measures to remedy the situation to the extent that any significant deficiencies are identified as a result of such inspection; and (d) with respect to any biological samples obtained from humans, obtain the appropriate informed consents in advance for the use of all such human biological samples, and use such samples at all times within the scope of the relevant informed consents;

(d) Neither Party shall, during the Term, grant any right or license or encumbrance or lien of any kind to any Third Party relating to any of the intellectual property rights it owns or Controls which would conflict or interfere with any of the rights or licenses granted or to be granted to the other Party hereunder pursuant to the provisions of Article 4 or by operation of the provisions of Article 12; and

(e) Each Party will notify the other Party in writing promptly in the event that it has actual knowledge of the material breach of any covenant under Section 10.2 or this Section 10.3 or the material breach of any representation or warranty provided by either Party under Section 10.1 or by TELETHON-HSR under Section 10.2.

Covenant of GSK

(f) GSK shall not use any of the intellectual property licensed to GSK under this Agreement outside the scope of the licenses granted under or granted pursuant to the provisions of this Agreement.

10.4 **Disclaimer.** Except as otherwise expressly set forth in this Agreement, NEITHER PARTY MAKES ANY REPRESENTATION OR EXTENDS ANY WARRANTY OF ANY KIND, EITHER EXPRESS OR IMPLIED, INCLUDING ANY WARRANTY THAT ANY PATENTS ARE VALID OR ENFORCEABLE OR THAT THEIR EXERCISE DOES NOT INFRINGE ANY PATENT RIGHTS OF THIRD PARTIES, AND EXPRESSLY DISCLAIMS ALL WARRANTIES OF MERCHANTABILITY AND FITNESS FOR A PARTICULAR PURPOSE. Without limiting the generality of the foregoing, each Party disclaims any warranties with regards to: (a) the success of any study or test commenced under this Agreement, (b) the safety or usefulness for any purpose of the technology or materials, including any Vectors, it provides or discovers under this Agreement; and/or (c) the validity, enforceability, or non-infringement of any intellectual property rights or technology it provides or licenses to the other Party under this Agreement.

11 INDEMNIFICATION; INSURANCE

11.1 **Indemnification by GSK.** GSK shall indemnify, defend and hold harmless TELETHON-HSR and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all liabilities, damages, losses, costs and expenses, including, but not limited to, the reasonable fees of attorneys (collectively, "**Losses**"), arising out of or resulting from any and all Third Party suits, claims, actions, proceedings or demands ("**Claims**") based upon:

(a) the negligence, recklessness or wrongful intentional acts or omissions of GSK and/or its Affiliates and/or Sublicensees and its or their respective directors, officers, employees and agents, in connection with GSK's performance of its obligations or exercise of its rights under this Agreement;

(b) any breach of any representation or warranty or express covenant made by GSK under Article 10; or

(c) the Development that is actually conducted by and/or on behalf of GSK (excluding any Development carried out by and/or on behalf of TELETHON-HSR hereunder), the handling and storage by and/or on behalf of GSK of any chemical agents or other Vectors for the purpose of conducting Development by or on behalf of GSK, and the manufacture, marketing, commercialization and sale by GSK, its Affiliate or Sublicensee of any Vector or GSK Product;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to the negligence, recklessness or wrongful intentional acts or omissions of TELETHON-HSR and/or its Affiliates and/Sublicensees, or their respective directors, officers, employees or agents.

11.2 **Indemnification by TELETHON-HSR.** For the indemnity obligations under this Section 11.2 and related provisions of Article 11 in relation to TELETHON-HSR, F. Telethon and F. San Raffaele shall be jointly and severally liable to GSK for all purposes. TELETHON-HSR shall indemnify, defend and hold harmless GSK and its Affiliates, and its or their respective directors, officers, employees and agents, from and against any and all Losses, arising out of or resulting from any and all Third Party Claims based upon:

(a) the negligence, recklessness or wrongful intentional acts or omissions of TELETHON-HSR and/or its Affiliates and/or its Sublicensees and/or its or their respective directors, officers, employees and agents, in connection with TELETHON-HSR's performance of its obligations or exercise of its rights under this Agreement;

(b) any breach of any representation or warranty or express covenant made by TELETHON-HSR under Article 10; or

(c) the Research and/or Development actually conducted by or on behalf of TELETHON-HSR (excluding any Research and Development carried out by or on behalf of GSK or its Affiliate, Sublicensee or subcontractor, provided however that the Research and Development which is to be carried out by or on behalf of TELETHON-HSR hereunder shall not be considered or interpreted to be Research and Development carried out by or on behalf of GSK), the handling and storage by and/or on behalf of TELETHON-HSR of any chemical agents or other Vectors or Products for the purpose of conducting Research and/or Development by or on behalf of TELETHON-HSR, and the manufacture, marketing, commercialization and sale by TELETHON-HSR, its Affiliate or Sublicensee of any Vector or Product or TELETHON-HSR Product;

except, in each case above, to the extent such Claim arose out of or resulted from or is attributable to the negligence, recklessness or wrongful intentional acts or omissions of GSK and/or its Affiliate and/or Sublicensees, or their respective directors, officers, employees and agents.

11.3 **Procedure.** In the event that any person (an "**Indemnitee**") entitled to indemnification under Section 11.1 or Section 11.2 is seeking such indemnification, such Indemnitee shall (i) inform, in writing, the indemnifying Party of the claim as soon as reasonably practicable after such Indemnitee receives notice of such claim, (ii) permit the indemnifying Party to assume direction and control of the defense of the claim (including the sole right to settle it at the sole discretion of the indemnifying Party, taking into consideration in good faith any reasonable concerns or objections raised by the Indemnitee; *provided that* such settlement does not impose any obligation on, or otherwise adversely affect, the Indemnitee or other Party), (iii) cooperate as reasonably requested (at the expense of the indemnifying Party) in the defense of the claim, and (iv) undertake all reasonable steps to mitigate any loss, damage or expense with respect to the claim(s).

11.4 **Settlement.** A settlement or consent judgment or other voluntary final disposition of a suit under this Article 11 may not be entered into without the prior written consent of the Party not bringing the suit, such consent not to be unreasonably withheld or delayed; provided that such settlement, consent judgment or other disposition does not admit the invalidity or unenforceability of the relevant Patent Rights in the TELETHON-HSR Patent Rights, GSK Patent Rights, or Joint Patent Rights, and provided

further, that any rights granted under the relevant Patent Rights to continue the infringing activity in such settlement, consent judgment or other disposition shall be limited to those rights that the granting Party otherwise has the right to grant, and provided further, that any settlement, consent judgment or other disposition shall not include the grant of any license, covenant or other rights to any Third Party that would limit or interfere with or reduce the scope of the subject matter included under the exclusive licenses to the ADA-SCID Program or to be granted to GSK pursuant to the exercise of any of its Options to Programs under Section 4.2, and further provided that such settlement does not impose any obligation on, or otherwise adversely affect the other Party.

11.5 Insurance.

(a) *TELETHON-HSR's Insurance Obligations*. For the insurance obligations under this Section 11.5 in relation to TELETHON-HSR under this Agreement, F. Telethon and F. San Raffaele shall be jointly and severally liable. TELETHON-HSR shall maintain, at its cost, with effect from the Effective Date and during the Term thereafter, adequate insurance against liability and other risks associated with its activities contemplated by this Agreement, including but not limited to its Clinical Trials and its indemnification obligations herein, in such amounts and on such terms as are customary for prudent practices in the biotechnology industry for the activities to be conducted by it under this Agreement.

(b) *GSK's Insurance Obligations*. GSK hereby represents and warrants to TELETHON-HSR that it is self-insured against liability and other risks associated with its activities and obligations under this Agreement in such amounts and on such terms as are customary for prudent practices for large pharmaceutical companies in the pharmaceutical industry for the activities to be conducted by it under this Agreement. GSK shall furnish to TELETHON-HSR evidence of such self-insurance upon written request.

11.6 **LIMITATION OF LIABILITY.** EXCEPT FOR A BREACH OF ARTICLE 9 OR FOR CLAIMS OF A THIRD PARTY THAT ARE SUBJECT TO INDEMNIFICATION UNDER THIS ARTICLE 11 OR AS OTHERWISE EXPRESSLY STATED IN THIS AGREEMENT, NEITHER TELETHON-HSR NOR GSK,

NOR ANY OF THEIR AFFILIATES WILL BE LIABLE TO THE OTHER PARTY TO THIS AGREEMENT OR ITS AFFILIATES FOR ANY INDIRECT, INCIDENTAL, CONSEQUENTIAL, SPECIAL, RELIANCE OR PUNITIVE DAMAGES OR LOST PROFITS, LOST DATA OR COST OF PROCUREMENT OF SUBSTITUTE GOODS OR SERVICES, WHETHER LIABILITY IS ASSERTED IN CONTRACT, TORT (INCLUDING NEGLIGENCE AND STRICT PRODUCT LIABILITY), INDEMNITY OR CONTRIBUTION, AND IRRESPECTIVE OF WHETHER THAT PARTY OR ANY REPRESENTATIVE OF THAT PARTY HAS BEEN ADVISED OF, OR OTHERWISE MIGHT HAVE ANTICIPATED THE POSSIBILITY OF, ANY SUCH LOSS OR DAMAGE.

12 TERM AND TERMINATION

12.1 **Term; Expiration.** This Agreement shall become effective as of the Effective Date and, unless earlier terminated pursuant to the other provisions of this Article 12, shall expire as follows:

(a) On a Product-by-Product and country-by-country basis, on the date of the expiration of all payment obligations under this Agreement with respect to such Product in such country;

(b) In its entirety upon the expiration of all payment obligations under this Agreement with respect to the last Product in all countries in the Territory; and

(c) On a Program-by-Program basis when no Vector or Product is being Researched, Developed or commercialized by either Party hereunder pursuant to a given Collaboration Program or GSK Development Program or TELETHON-HSR Development Program.

The period from the Effective Date until the date of expiration of this Agreement in its entirety, or as the case may be, until the date of the expiration of this Agreement in part with respect to a given Product or Program, may be referred to herein as the "**Term.**"

12.2 **Termination for Cause.**

(a) *Termination for Material Breach*. Either Party (the "**Non-breaching Party**") may, without prejudice to any other remedies available to it at law or in equity, terminate this Agreement, either on a Program-by-Program basis or in its entirety, as may be appropriate to protect the interest of the Non-breaching Party arising from such alleged breach, in the event the other Party (the "**Breaching Party**") shall have breached or defaulted in the performance of any of its material obligations hereunder either with respect to a particular Program or the Agreement as a whole, and such default shall have continued for [***] after written notice thereof was provided to the Breaching Party by the Non-breaching Party, such notice describing with particularity and in detail the alleged material breach. Subject to Section 12.2(b), any such termination of the Agreement under this Section 12.2 shall become effective at the end of such [***] period, unless the Breaching Party has cured any such breach or default prior to the expiration of such [***] period, or if such breach is not susceptible to cure within such [***] period even with the use of Commercially Reasonable Efforts, the Non-Breaching Party's right to termination shall be suspended only if and for so long as the Breaching Party has provided to the Non-Breaching Party a written plan that is reasonably calculated to effect a cure, such plan is acceptable to the Non-Breaching Party (or to the arbitrators, in the event of arbitration pursuant to Section 13.2), and the Breaching Party commits to and does carry out such plan. The right of either Party to terminate this Agreement or a portion of this Agreement, as provided in this Section 12.2 shall not be affected in any way by such Party's waiver or failure to take action with respect to any previous default.

(b) *Disagreement.* If the Parties reasonably and in good faith disagree as to whether there has been a material breach, the Party that seeks to dispute that there has been a material breach may contest the allegation in accordance with Section 13.1. The cure period for any allegation made in good faith as to a material breach under this Agreement will run from the date that written notice was first provided to the Breaching Party by the Non-breaching Party, but shall be suspended if so agreed or ordered pursuant to Sections 13.1 and 13.2.

12.3 **GSK Unilateral Termination Rights; and Termination Rights of Either Party for Safety Reasons.**

(a) *GSK's Unilateral Termination Rights for any Reason*. GSK shall have the right, at its sole discretion and without any penalty or liability, exercisable at any time during the Term, to terminate this Agreement either in its entirety, or on a Program-by-Program basis for one or more Programs, for any reason or for no reason at all, upon [***] prior written notice to TELETHON-HSR, in each case subject to the obligations set forth in Section 12.5(b). It is understood that GSK has no rights for refund of any payment made to TELETHON-HSR. For the avoidance of doubt, if GSK exercises its right to terminate pursuant to this Section 12.3, it shall not be entitled to a refund in respect of any sums already paid to TELETHON-HSR.

(b) *Termination Rights of Either Party for Safety Reasons*. Each Party shall have the right, for compelling safety reasons which could not be resolved at the Joint Development Committee in accordance with the procedure set forth in Section 3.2(h), to terminate its involvement in any Collaboration Program with immediate effect, or, with effect as soon as is practicable, where a study is ongoing and it would be unethical to terminate such study immediately. In case of any such dispute not resolved by the Joint Development Subcommittee as described in Section 3.2(h) as to whether or not to initiate any clinical study in humans, (a) if the safety concern was originally raised by TELETHON-HSR, the Collaboration Program shall be suspended, and may be resumed by or on behalf of TELETHON-HSR only under the terms and conditions of this Agreement as a resumed Collaboration Program (and TELETHON-HSR may not resume such program independently or in collaboration with a Third Party during the Term), or (b) if the safety concern was originally raised by GSK and relates to whether or not to initiate any clinical study in humans or as to whether or not any Clinical Study protocol or any aspect of monitoring thereof for Phase I Clinical Studies proposed by TELETHON-HSR is safe, the Collaboration Program will be terminated and TELETHON-HSR shall be free to proceed in its own name and with Third Parties with regard to such Collaboration Program.

12.4 **Termination for Insolvency**. Either Party may terminate this Agreement if, at any time, the other Party shall file in any court or agency pursuant to any statute or regulation of any state or country, a petition in bankruptcy or insolvency or for reorganization (other than reorganization by virtue of mergers or consolidations with any other entity or as a result of any other transaction or series of transactions (such as a listing on a public recognised stock exchange or fund raising from existing or new investors) all in the ordinary course of business) or for an arrangement or for the appointment of a receiver or trustee of the Party or of substantially all of its assets, or if the other Party proposes a written agreement of composition or extension of substantially all of its debts (other than in the ordinary course of business), or if the other Party shall be served with an involuntary petition against it, filed in any insolvency proceeding, and such petition shall not be dismissed within [***] after the filing thereof, or if the other Party shall propose or be a Party to any dissolution or liquidation, or if the other Party shall make an assignment of substantially all of its assets for the benefit of creditors.

12.5 **Effect of Termination or Expiration**.

(a) *Upon Expiration.* Following the expiration of the Term pursuant to Section 12.1, the following terms shall apply:

(i) Subject to the terms and conditions of this Agreement, following expiration of the Term with respect to a GSK Product in a country pursuant to Section 12.1(a), GSK shall have an exclusive, fully-paid and royalty-free right and license, with the right to grant sublicenses, under the Exclusively Licensed IP solely to continue to make, have made, use, sell, offer to sell and import such GSK Product in the Field in such country, for so long as it continues to do so.

(ii) Subject to the terms and conditions of this Agreement, following expiration of the Term with respect to a TELETHON-HSR Product in a country pursuant to Section 12.1(a), TELETHON-HSR shall have an exclusive, fully-paid and royalty-free right and license, with the right to grant sublicenses, under the GSK IP and GSK's share in any Joint IP solely to continue to make, have made, use, sell, offer to sell and import such TELETHON-HSR Product in the Field in such country, for so long as it continues to do so.

(iii) Subject to the terms and conditions of this Agreement, following expiration of the Term with respect to this Agreement in its entirety pursuant to Section 12.1(b), GSK shall have an exclusive, fully-paid and royalty-free right and license, with the right to grant sublicenses, under the Exclusively Licensed IP, solely to continue to make, have made, use, sell, offer to sell and import GSK Products in the Field in the Territory, for so long as it continues to do so.

(iv) Subject to the terms and conditions of this Agreement, following expiration of the Term with respect to this Agreement in its entirety pursuant to Section 12.1(b), TELETHON-HSR shall have an exclusive, fully-paid and royalty-free right and license, with the right to grant sublicenses, under the GSK IP and GSK's share in any Joint IP solely to continue to make, have made, use, sell, offer to sell and import TELETHON-HSR Products in the Field in the Territory, for so long as it continues to do so.

(b) *Upon Unilateral Termination by GSK.* In the event of a unilateral termination of this Agreement in its entirety or any Program by GSK pursuant to Sections 5.2(b), 7.2 or 12.3, the following terms shall apply:

(i) Notwithstanding anything contained herein to the contrary, all licenses granted to GSK with respect to Vectors and GSK Products in the terminated Program (or, in the case of termination of the entire Agreement, all Vectors and GSK Products) shall terminate, each such GSK Product shall be deemed to be a TELETHON-HSR Product and TELETHON-HSR shall have the exclusive right, at its sole discretion, to further Develop and commercialize such TELETHON-HSR Product in the Territory in the Field, alone or with any Third Party or through any Sublicensee, Affiliate or subcontractor

without any obligation to GSK, subject to the applicable payment obligations under Section 6.5; GSK will be obligated to pay any uncancellable and incurred charges under a Collaboration Program that cannot be avoided by TELETHON-HSR as mitigation of costs during the [***] period after notice of termination for winding down of the relevant Program, provided however, that GSK shall not be obligated to pay any additional amounts that would amount to being a penalty for such termination;

(ii) as of the date of notice of such termination, GSK shall not be required to use Commercially Reasonable Efforts to progress any GSK Products in the terminated Program(s) under this Agreement, and as of the effective date of such termination, GSK will cease any and all Development and commercialization activities with respect to Vectors included in a terminated Program (or in the case of termination of the entire Agreement, all Programs); provided, however, that nothing in this Section 12.5(b) is intended to limit GSK's obligations under Section 12.5(e);

(iii) All unexercised Options with respect to the terminated Program(s) as of the date that TELETHON-HSR receives such notice from GSK shall be cancelled and of no force and effect;

(iv) With respect to any Product in a terminated Program (or in the case of termination of the entire Agreement, all Programs), GSK shall grant, and hereby grants, to TELETHON-HSR an exclusive right and license, with the right to grant sublicenses, under GSK's share in any Joint IP solely to Develop, make, have made, use, sell, offer to sell and import such Vector as a TELETHON-HSR Product in the Field in the Territory, for so long as it, its Affiliates, subcontractors and/or Sublicensees continues to do so, and TELETHON-HSR shall have the exclusive right, at its sole discretion, to further Develop and commercialize such Vector as a TELETHON-HSR

Product in the Territory in the Field, alone or with any Third Party or through any Sublicensee, Affiliate or subcontractor without any obligation to GSK, and TELETHON-HSR shall have the right to negotiate in good faith and on commercially reasonable terms for a license under the relevant GSK IP solely as required to further Develop and commercialize such TELETHON-HSR Products in the Field and in the Territory.

(c) *Upon Termination by GSK for Cause or for TELETHON-HSR's Insolvency*. In the event of a termination of this Agreement in its entirety or any Program by GSK pursuant to Section 12.2(a) for a material breach by TELETHON-HSR, or the entire Agreement pursuant to Section 12.4, the following consequences shall apply, provided however, that no termination shall be effective, and no consequences under this Section 12.5(c) shall be implemented until a final determination under the provisions of Article 13 has been made with regard to any dispute by a Party as to the existence of an uncured material breach:

(i) All Options with respect to the terminated Programs (or in the case of termination of the entire Agreement, all Options) that are unexercised as of the effective date of termination shall automatically become exercisable, on the effective date of termination, by GSK in accordance with Section 4.2 by written notice to TELETHON-HSR and upon such exercise, the exclusive licence to be granted with respect to each Collaboration Program to which the Option is being exercised in Section 4.2 shall immediately become effective and TELETHON-HSR hereby grants such exclusive licences to GSK conditional upon the occurrence of such event. Any Options which are not so exercised upon termination pursuant to this Section 12.5(c)(i) shall be cancelled and of no further force or effect. In respect of any Option which is exercised as a result of the termination, GSK's obligations to pay the Option Exercise Fee and any milestone payments that would otherwise be applicable under the provisions of Section 6.2 shall all be cancelled, and the royalty payments that would otherwise be applicable under the provisions of Section 6.3 shall all be reduced by [***].

(ii) In the case of termination by GSK of a Program for an uncured material breach or insolvency of TELETHON-HSR that occurred after the exercise by GSK of its Option with respect to such Program or a termination by GSK of the entire Agreement, in each case pursuant to Section 12.2(a) or Section 12.4, GSK shall retain any exclusive licenses granted in Section 4.1 or 4.2 with respect to the Vectors and Products in each terminated Program for which GSK has already exercised its Option and GSK shall have the right to exercise any unexercised Options, and GSK's obligations under Article 6 to make any milestone payments shall remain unchanged, and the royalty payments that would otherwise be applicable under the provisions of Section 6.3 shall all be reduced by [***].

(iii) In the event of termination of the Agreement in its entirety or on a Program-by-Program basis by GSK pursuant to Section 12.2(a), TELETHON-HSR shall comply with its obligations under Section 4.14 for each terminated Program and all obligations of TELETHON-HSR under Article 7 shall continue in full force and effect on a Collaboration Program–by-Collaboration Program basis in accordance with its terms;

(iv) GSK shall cease to have any obligations with respect to diligence or to use Commercially Reasonable Efforts with respect to (i) any Vectors or GSK Products resulting from any Collaboration Program or any GSK Development Program that was terminated by GSK pursuant to Section 12.2(a), or (ii) all Vectors and GSK Products if the entire Agreement was terminated pursuant to Section 12.2(a) or 12.4.

(d) *Upon Termination by TELETHON-HSR for Cause or GSK's Insolvency*. In the event that TELETHON-HSR terminates a Program or this Agreement pursuant to Section 12.2(a) or the entire Agreement pursuant to Section 12.4, the following consequences shall apply, provided however, that no termination shall be effective, and no consequences under this Section 12.5(d) shall be implemented until a final determination under the provisions of Article 13 has been made with regard to any dispute by a Party as to the existence of an uncured material breach:

(i) All Options with respect to the terminated Programs (or in the case of termination of the entire Agreement, all Options) that are unexercised as of the effective date of termination shall be cancelled and of no force and effect. For clarity, GSK shall not be permitted to exercise any Option after receiving notice of TELETHON-HSR's termination under Section 12.2(a) without TELETHON-HSR's prior written consent, unless and until TELETHON-HSR agrees, or it is determined pursuant to the process set forth under Section 13.1 or Section 13.2, that GSK has cured the applicable breach in a timely manner or GSK has not been in material breach or GSK has been in breach but the matter has been resolved in favor of allowing GSK to exercise its Option;

(ii) With respect to any Vector or Product in a terminated Program (or in the case of termination of the entire Agreement, any Program), at TELETHON-HSR's option, GSK will grant, and hereby grants, to TELETHON-HSR an exclusive royalty free right and license, with the right to grant sublicenses, under GSK's share in any Joint IP solely to Develop, make, have made, use, sell, offer to sell and import such Vectors as TELETHON-HSR Products in the Field in the Territory, for so long as it, its Affiliates, subcontractors and Sublicensees continues to do so, and TELETHON-HSR shall have the exclusive right, at its sole discretion, to further Develop and commercialize such Vector as a TELETHON-HSR Product in the Territory in the Field, alone or with any Third Party or through any Sublicensee, Affiliate or subcontractor without any obligation to GSK. In addition, TELETHON-HSR shall have the right to negotiate with GSK in good-faith and on commercially-reasonable terms for a license to use GSK IP as necessary solely for the purpose of Development and commercialization of such TELETHON-HSR Products in the Territory and in the Field.

(e) *Obligations of GSK with Respect to Vectors in TELETHON-HSR Products.* Upon termination of a Program or this Agreement by TELETHON-HSR pursuant to Section 12.2(a) or the termination of the entire Agreement by TELETHON-HSR pursuant to Section 12.4, or termination of a Program or this Agreement by GSK pursuant to Section 12.3:

(i) GSK shall complete any ongoing trials of GSK Products; provided, however, that if TELETHON-HSR terminates this Agreement pursuant to Sections 12.2(a) or 12.4, TELETHON-HSR may instead elect to have GSK (i) transition oversight of such ongoing trials to TELETHON-HSR as soon as reasonably practicable and in any event within [***] and (ii) GSK shall reimburse TELETHON-HSR for all costs associated with TELETHON-HSR completing such trials. Notwithstanding the foregoing, GSK may prematurely suspend or terminate any such trial if (A) a priori protocol defined stopping rules are met for safety or efficacy or (B) unacceptable safety signals are observed by the Data and Safety Monitoring Board with respect to the Product or related Vector that present an unacceptable risk to patients participating in such trials;

(ii) GSK shall promptly and in any event within [***] return to TELETHON-HSR, free of charge, all Know-How and materials transferred by TELETHON-HSR to GSK with respect to each such Vector and shall transfer stocks of Product free of charge to TELETHON-HSR;

(iii) GSK shall transfer to TELETHON-HSR within [***], at TELETHON-HSR's request, any and all data and Know-How pertaining to the applicable Vectors that are necessary for the continued Development and commercialization of such Vectors in its possession and other related materials, including without limitation copies of all Clinical Trial data and results, and all other Know-How and the like developed by or for the benefit of GSK relating to such Vectors and other documents to the extent relating to such Vectors that are necessary in the continued Development and

commercialization of such Vectors as TELETHON-HSR Products (including without limitation material documents and agreements relating to the sourcing, manufacture, promotion, distribution, sale or use of a Product) throughout the Territory; and

(iv) GSK will transfer and assign ownership of all regulatory filings and approvals relating to such Vectors (including any NDAs) to TELETHON-HSR (or its designated Affiliate), and send any correspondence to regulatory authorities, execute any instruments, or take any other steps TELETHON-HSR reasonably deems necessary to effectuate such transfers.

12.6 **Accrued Rights; Surviving Provisions of the Agreement**.

(a) Termination, relinquishment or expiration of this Agreement for any reason shall be without prejudice to any rights that shall have accrued to the benefit of any Party prior to such termination, relinquishment or expiration including the payment obligations under Article 6 hereof and any and all damages or remedies arising from any breach hereunder. For clarity, all payment obligations which have accrued and are due as of the termination, relinquishment or expiration date shall immediately become due and payable. Such termination, relinquishment or expiration shall not relieve any Party from obligations which are expressly indicated to survive termination of this Agreement.

(b) The provisions of Articles 9, 11 and 13, 4 (by operation of the provisions of Section 12.5 as applicable), Sections 5.2 and 5.3 (by operation of the provisions of Section 12.5, as applicable), Sections 6.2 -6.11 (by operation of the provisions of Section 12.5, as applicable), 8.1, 8.4, 8.5, 10.4, 12.5, 12.6 and 13.2, as well as any applicable definitions in Article 1, shall survive the termination or expiration of this Agreement for any reason, in accordance with their respective terms and conditions, and for the duration stated, and where no duration is stated, shall survive indefinitely. Article 9 shall survive for a period of [***].

13 MISCELLANEOUS

13.1 **Dispute Resolution.**

(a) Except to the extent that a Party has final decision-making authority under Section 3.1 or 3.2(d), or to the extent that such dispute is subject to final resolution by the Executive Officers under Section 3.2(i), the Parties agree to resolve any controversy, claim or dispute arising under this Agreement pursuant to this Article 13. Either Party may refer such dispute to the respective Executive Officers, and such Executive Officers shall attempt in good faith to resolve such dispute. If the Parties are unable to resolve a given dispute pursuant to this Section 13.1 within [***] of referring such dispute to the Executive Officers, either Party may refer the dispute for mediation pursuant to Section 13.1(b) below.

(b) If either Party refers a dispute to mediation pursuant to Section 13.1 (a) above, the Parties will endeavor to settle the dispute by mediation under the ICC International Institute for Conflict Prevention and Resolution ("CPR") Mediation Procedure then currently in effect. If one Party fails to participate in the negotiation as provided in above, the other Party can initiate mediation prior to the expiration of the [***] period referenced in Section above. Unless otherwise agreed, the Parties will attempt to select a mediator from the CPR Panels of Distinguished Neutrals. If the Parties cannot agree on a mediator, they will defer to the CPR, which shall select a mediator for them. The cost of the mediator shall be divided equally between the Parties. If the Parties cannot reach agreement within [***] after the appointment of a mediator, either Party may demand that the given dispute be resolved by binding Arbitration pursuant to Section 13.2 (the "**Arbitration Demand**").

(c) Where a Party has final decision-making authority under Section 3.1 or 3.2(d), or such dispute is subject to final resolution by the Executive Officers under Section 3.2(d), such final decision or resolution shall not be subject to further review under this Agreement or otherwise under law or equity, provided, however, that such final decision-making shall not constitute a waiver by the other Party of any of its rights or remedies for breach of this Agreement in law or equity.

(d) In the event of a dispute between the Parties arising under Section 2.6(b), the matter shall first be referred to the Executive Officers for resolution under Section 13.1(a), and if not resolved, shall be referred to a mutually agreed independent Third Party expert with expertise in the issue under dispute who shall be instructed to determine such dispute in a manner consistent with good industry standards in the biopharmaceutical industry. In the event that the Parties are unable to agree on the identity of an independent Third Party expert within [***], either Party may request that the Director General of the Association of the British Pharmaceutical Industry and/or the Chairman of the BioIndustry Association (BIA) recommend a potential expert or a list of potential experts, provided such person(s) is not affiliated or otherwise associated with either Party, and does not have any conflict of interest in relation to either Party or in relation to the subject of the dispute, unless waived in writing by the other Party. The Parties shall review such recommendations to determine a mutually agreed Third Party expert. Once the expert has been mutually agreed upon by the Parties, the Parties will cooperate with expert and comply with any procedural rules or requests made by the expert. The expert's determination shall be final, and all costs shall be shared equally by the Parties.

13.2 **Arbitration**

All disputes and differences arising out of, or in connection with, this Agreement shall be finally settled under the Rules of Arbitration of the International Chamber of Commerce (the "**Rules**") by [***] arbitrators, unless the Parties mutually agree in writing in advance that given the nature of the dispute and the amount in dispute, [***] arbitrator will be acceptable for use instead of using three arbitrators. Each Party shall appoint one arbitrator in accordance with the Rules, and the two arbitrators so appointed shall appoint the third (and presiding) arbitrator in accordance with the Rules within [***] from the confirmation of the appointment of the party-appointed arbitrators. The place of arbitration shall be [***]. The language of the arbitration shall be English. In the event of an inability to agree on a third arbitrator or failure to

\notify the other Party and the ICC of that nomination within the above-mentioned time limit, the appointing of the presiding arbitrator shall be made by the International Court of Arbitration of the International Chamber of Commerce, acting in accordance with the Rules.

(a) The arbitrators shall have the authority to grant any interim award and to order any interim or permanent relief as they may deem necessary or advisable under the circumstances, including, but not limited to, a grant of injunctive relief or an order of specific performance.

(b) The Parties shall bear equally the costs and expenses of arbitration, and each such Party shall bear the costs and expenses of its own counsel, technical advisors and expert witnesses, unless the decision of the arbitrators shall otherwise direct.

(c) Any arbitration award or any interim relief or award rendered in accordance with this Section 13.2 shall be satisfied promptly and without the need for the prevailing Party to seek enforcement, which may be sought in any court having competent jurisdiction. In the event resort to enforcement proceedings are required for any interim or final award or decision, the Party which has not complied with the arbitral award or decision, whether interim or final, shall be responsible for both Parties' reasonable attorneys' fees and all direct costs in the enforcement proceeding.

13.3 **Governing Law.** This Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

13.4 **Assignment.** Either Party may assign this Agreement to any Affiliate of such Party without the consent of the other Party; provided, that such Party provides the other Party with written notice of such assignment and remains fully liable for the performance of such Party's obligations hereunder by such Affiliate. Further, each Party may assign this Agreement without the consent of the other Party to its successor in interest by way of merger, acquisition, or sale of all or substantially all of its assets to which one or more Programs of this Agreement relates; provided, that

such Party provides the other Party with written notice of such assignment; provided further, that if such assignment involves a Change of Control Event, then TELETHON-HSR will notify GSK prior to the closing of such Change of Control Event and GSK shall have the rights set out in Section 4.8 (a). The terms and conditions of this Agreement shall be binding upon and shall inure to the benefit of the successors, heirs, administrators and permitted assigns of the Parties. Any purported assignment in violation of this Section 13.4 shall be null and void.

13.5 **Performance Warranty.** Each Party hereby acknowledges and agrees that it shall be responsible for the full and timely performance as and when due under, and observance of all the covenants, terms, conditions and agreements set forth in this, Agreement by its Affiliate(s) and Sublicensees.

13.6 **Force Majeure.** No Party shall be held liable or responsible to the other Party nor be deemed to be in default under, or in breach of any provision of, this Agreement for failure or delay in fulfilling or performing any obligation (other than a payment obligation) of this Agreement when such failure or delay is due to *force majeure*, and without the fault or negligence of the Party so failing or delaying. For purposes of this Agreement, *force majeure* is defined as causes beyond the control of the Party, including acts of God; acts, acts of terrorism, regulations, or laws of any government; war; civil commotion; destruction of production facilities or materials by fire, flood, earthquake, explosion or storm; labor disturbances; epidemic; and failure of public utilities or common carriers. In such event TELETHON-HSR or GSK, as the case may be, shall immediately notify the other Party of such inability and of the period for which such inability is expected to continue. The Party giving such notice shall thereupon be excused from such of its obligations under this Agreement as it is thereby disabled from performing for so long as it is so disabled for up to a maximum of [***], after which time TELETHON-HSR and GSK shall promptly meet to discuss in good faith how to best proceed in a manner that maintains and abides by the Agreement. To the extent possible, each Party shall use reasonable efforts to minimize the duration of any *force majeure.*

13.7 **Notices.** Any notice or request required or permitted to be given under or in connection with this Agreement shall be deemed to have been sufficiently given if in writing and personally delivered or sent by certified mail (return receipt requested), facsimile transmission (receipt verified), or overnight express courier service (signature required), prepaid, to the Party for which such notice is intended, at the address set forth for such Party below:

If to TELETHON-HSR, addressed to:

For F. Telethon, addressed to:

[***]

For F. San Raffaele, addressed to:

[***]

If to GSK:

Attention: [***]

with a copy to: [***]

or to such other address for such Party as it shall have specified by like notice to the other Parties, provided that notices of a change of address shall be effective only upon receipt thereof. If delivered personally or by facsimile transmission, the date of delivery shall be deemed to be the date on which such notice or request was given. If sent by overnight express courier service, the date of delivery shall be deemed to be the next Business Day after such notice or request was deposited with such service. If sent by certified mail, the date of delivery shall be deemed to be the [***] after such notice or request was deposited with the U.S. Postal Service.

13.8 **Waiver.** Neither Party may waive or release any of its rights or interests in this Agreement except in writing. The failure of either Party to assert a right hereunder or to insist upon compliance with any term or condition of this Agreement shall not constitute a waiver of that right or excuse a similar subsequent failure to perform any such term or condition. No waiver by either Party of any condition or term in any one or more instances shall be construed as a continuing waiver of such condition or term or of another condition or term.

13.9 **Severability.** If any provision hereof should be held invalid, illegal or unenforceable in any jurisdiction, the Parties shall negotiate in good faith a valid, legal and enforceable substitute provision that most nearly reflects the original intent of the Parties and all other provisions hereof shall remain in full force and effect in such jurisdiction and shall be liberally construed in order to carry out the intentions of the Parties hereto as nearly as may be possible. Such invalidity, illegality or unenforceability shall not affect the validity, legality or enforceability of such provision in any other jurisdiction.

13.10 **Entire Agreement.** This Agreement, together with the Schedules and Exhibits hereto, set forth all the covenants, promises, agreements, warranties, representations, conditions and understandings between the Parties hereto and supersede and terminate all prior agreements and understanding between the Parties. There are no covenants, promises, agreements, warranties, representations, conditions or understandings, either oral or written, between the Parties other than as set forth herein and therein. No subsequent alteration, amendment, change or addition to this Agreement shall be binding upon the Parties hereto unless reduced to writing and signed by the respective authorized officers of the Parties.

13.11 **Independent Contractors.** Nothing herein shall be construed to create any relationship of employer and employee, agent and principal, partnership or joint venture between the Parties. Each Party is an independent contractor. Neither Party shall assume, either directly or indirectly, any liability of or for the other Party. Neither Party shall have the authority to bind or obligate the other Party and neither Party shall represent that it has such authority.

13.12 **Headings; Interpretation.** Headings used herein are for convenience only and shall not in any way affect the construction of or be taken into consideration in interpreting this Agreement. Further, in this Agreement: (a) the word “including” shall be deemed to be followed by the phrase “without limitation” or like expression; (b) the singular shall include the plural and vice versa; and (c) masculine, feminine and neuter pronouns and expressions shall be interchangeable.

13.13 **Books and Records.** Any books and records to be maintained under this Agreement by a Party or its Affiliates or Sublicensees shall be maintained in accordance with Dutch generally accepted accounting principles or International Financial Reporting Standards (IFRS) in the case of TELETHON-HSR, and shall be maintained in accordance with IFRS in the case of GSK, consistently applied, except that the same need not be audited.

13.14 **Further Actions.** Each Party shall execute, acknowledge and deliver such further instruments, and do all such other acts, as may be reasonably necessary or appropriate in order to carry out the expressly stated purposes and the clear intent of this Agreement.

13.15 **Parties in Interest.** All of the terms and provisions of this Agreement shall be binding upon, and shall inure to the benefit of and be enforceable by the Parties hereto and their respective successors, heirs, administrators and permitted assigns.

13.16 **Contracts (Rights of Third Parties) Act 1999.** A person (other than an Affiliate) who is not a Party to this Agreement has no right under the Contracts (Rights of Third Parties) Act 1999 to enforce any term of this Agreement, but this does not affect any right or remedy of a third Party which exists or is available apart from that Act.

13.17 **Construction of Agreement.** The terms and provisions of this Agreement represent the results of negotiations between the Parties and their representatives, each of which has been represented by counsel of its own choosing, and neither of which has acted under duress or compulsion, whether legal, economic or otherwise. Accordingly, the terms and provisions of this Agreement shall be interpreted and construed in accordance with their usual and customary meanings, and each of the Parties hereto hereby waives the application in connection with the interpretation and construction of this Agreement of any rule of law to the effect that ambiguous or conflicting terms or provisions contained in this Agreement shall be interpreted or construed against the Party whose attorney prepared the executed draft or any earlier draft of this Agreement.

13.18 **Supremacy.** In the event of any express conflict or inconsistency between this Agreement and a Development Plan or any Schedule or Exhibit hereto, the terms of this Agreement shall control. The Parties understand and agree that the Schedules and Exhibits hereto are not intended to be the final and complete embodiment of any terms or provisions of this Agreement, and are to be updated from time to time during the Term, as appropriate and in accordance with the provisions of this Agreement.

13.19 **Counterparts.** This Agreement may be signed in counterparts, each and every one of which shall be deemed an original, notwithstanding variations in format or file designation which may result from the electronic transmission, storage and printing of copies of this Agreement from separate computers or printers. Facsimile signatures and signatures transmitted via PDF shall be treated as original signatures.

[Signature page to follow]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Research and Development Collaboration and License Agreement to be executed by their duly authorized representatives as of the Effective Date.

For TELETHON-HSR:

Fondazione Telethon

By: [***]

Name: [***]

Title: [***]

Fondazione Centro San Raffaele del Monte Tabor

By: [***]

Name: [***]

Title: [***]

For GSK:

Glaxo Group Limited

By: [***]

Name: [***]

Title: [***]

Exhibit A
General Guidelines for Clinical Candidate Selection Criteria

Vector characterization
[***]

Pharmacokinetics
[***]

Pharmacodynamics
[***]

Toxicology
[***]

Exhibit B
Example of Data and Documents to be Transferred under Sec. 2.9(c)

Where GSK acquires an exclusive license to develop a Vector or Product and previous studies likely to be required for regulatory submission were conducted by Telethon, Telethon will transfer the following documents and materials where applicable / available.

Regulatory

[***]

Safety

[***]

Clinical

[***]

Data Management

[***]

[***]

Special Analysis & Publishing

[***]

*** Confidential Treatment Requested ***

Exhibit C

Proof of Concept Criteria

[***]

Exhibit D
TELETHON-HSR Patent list

[***]

Exhibit E
Research Program for LV Platform Improvements

Objectives

[***]

TELETHON-HSR Commitment

[***]

GSK Commitment

[***]

Exhibit F
Research Program for Vector Manufacturing Improvements

This is split into two broad categories:

1 – [***]

TELETHON-HSR Commitment

[***]

GSK Commitment

[***]

[***]

TELETHON-HSR Commitment

[***]

GSK Commitment

[***]

AMENDMENT NO. 1 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 1 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 1**") is entered into as of this 31 day of March 2015 (the "**Amendment No. 1 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline Intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 1 amends that certain Research and Development Collaboration and License Agreement (the "**Collaboration Agreement**") entered into on October 15, 2010 between GGL, Telethon and Fondazione Centro San Raffaele del Monte Tabor. Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "**Party**" and collectively as the "**Parties**." Telethon and OSR may be referred to herein collectively as "**Telethon-HSR**".

WHEREAS, the Parties are collaborating on several Collaboration Programs for *ex vivo* hematopoietic stem cell gene therapy of monogenic diseases, including a Collaboration Program in Beta-thalassemia (the "**Beta-Thal Program**");

WHEREAS, Telethon-HSR is responsible for the conduct of Research and Development activities as set forth in the Development Plan for the Beta-Thal Program up through and including completion of the Proof of Concept Study;

WHEREAS, GSK has an exclusive option right to exclusively in-license the Beta-Thal Program;

WHEREAS, the Parties have agreed to make certain modifications to the Development Plan for the Beta-Thal Program, including modifying the Development Plan to include up to [***] patients to the Beta-Thal Program protocol for the first [***] clinical study as briefly summarized in the attached Exhibit D;

WHEREAS Telethon-HSR has developed in the course of preclinical studies [***], here after referred to as "[***]", and has filed a patent application on such [***] (namely the [***], together with -without limitation- any patents issuing therefrom, any patent applications and/or issued patents claiming priority thereto, and any reissues, re-examinations, divisionals, continuations, and continuations in part arising therefrom in any jurisdiction, shall be referred to hereinafter as the "**[***]**").

WHEREAS the Parties agreed to activate an improvement project referred to as the "[***]" as defined in Section 2 in this Amendment No. 1, to include up to [***] additional patients.

WHEREAS, the Parties have further agreed that GSK will pay an access fee of [***] to activate the [***], as expressly set forth in this Amendment No. 1;

WHEREAS, the Parties have previously entered into several side letter agreements related to the ADA-SCID Program and to other Collaboration Programs under the Collaboration Agreement and now also desire to include all such side letters by reference into this Amendment No. 1 to ensure that each of such side letter agreements are captured as amendments to the Collaboration Agreement; and

WHEREAS, the Parties now desire to enter into this Amendment No. 1 to capture their agreement with respect to the above referenced subject matters, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

*** Confidential Treatment Requested ***

1. Additional Pre-Clinical Work for [***]. Clause 2.4(a)(i) of the Collaboration Agreement shall be amended, solely with respect to the Beta-Thal Program, to add the following:

"In consideration of the [***] Access Fee to be paid by GSK to Telethon-HSR as set forth in Section 6{a) of this Amendment No.1, following the Amendment No. 1 Effective Date, Telethon-HSR will apply the [***] to the Beta-Thal Program and such application will become part of the Beta- Thal Program and as such managed according to the Collaboration Agreement. The Parties acknowledge that, prior to Amendment No. 1 Effective Date, Telethon-HSR provided the data and results from the study to the JSC. Moreover Telethon-HSR will continue pre-clinical development as set forth more fully on **Exhibit B** to Amendment No. 1 (the "**Preclinical Development**"). Upon completion of the Preclinical Development, Telethon-HSR will provide the data and results to the JSC."

2. [***]—Pre-Clinical Activities. Clause 2.4(c) of the Collaboration Agreement shall be amended, solely with respect to the Beta-Thal Program to add the following new Clause 2.4(c)(iv):

"2.4(c)(iv)(A) GSK and Telethon-HSR are collaborating in the development of protocols, Assays and Reagents with the goal of establishing a GMP Production Protocol and GMP Clinical Protocol for use in the [***] for the Beta-Thal Program (the "**[***]**"). In furtherance of this goal, Telethon-HSR provided the needed information on specifications around [***], as well as on data with use of research reagents in order to [***], and on function of the cells in vitro and in vivo (mouse models) to allow GSK to conduct certain additional activities in connection thereto also through a third party CMO; specifically, additional activities regarding further development of the [***] protocol for the [***], either using [***] (collectively, the "**Additional GMP Protocol Work**"). For purposes of this Amendment No. 1, the following terms shall be defined to mean:

'**Reagents**' means antibodies, beads and cell line(s);

‘**Assays**’ means FACS, colony assays, other assays as necessary to [***] the cells.

‘**GMP Production Protocol**’ means the GMP production protocol to [***].

‘**GMP Clinical Protocol**’ means the GMP clinical protocol to [***],

(B) ***Ownership; Licenses***. Telethon-HSR and GSK shall jointly own in equal shares the results of the Additional GMP Protocol Work and any intellectual and industrial property rights arising in the conduct of the Additional GMP Protocol Work for which, as between GSK and its third party CMO, are owned by GSK (“**Additional GMP Protocol Work IP**”) and both Telethon-HSR and GSK may use such results for any and all purposes. Each Party hereby grants to the other Party a non-exclusive, royalty-free, right and license under such Party’s rights and interest in the Additional GMP Protocol Work IP for any use, subject to the following: (i) with respect to those Collaboration Programs for which GSK has exercised its Option under the Collaboration Agreement the license granted by Telethon-HSR to GSK under Telethon-HSR’s rights in the Additional GMP Protocol Work IP shall be an exclusive license with respect to use of the Additional GMP Protocol Work IP for such Collaboration Program; and (ii) with respect to those Collaboration Programs for which GSK has not yet exercised its Option, upon GSK’s Option exercise for such Collaboration Program, the license granted by Telethon-HSR to GSK under Telethon-HSR’s rights in the Additional GMP Protocol Work IP shall automatically be converted to an exclusive license with respect to the use of the Additional GMP Protocol Work IP for such Collaboration Program.

With no prejudice to Clause 2.11 of the Collaboration Agreement, to the extent that the results and/or the Additional GMP Protocol Work IP (as applicable) contains any intellectual or industrial property rights of the third party CMO that are necessary to use the results and/or the Additional GMP Protocol Work IP (as applicable), GSK will use reasonable efforts to obtain the rights to extend any CMO licenses that have been granted to GSK to Telethon-HSR.

For purposes of this Amendment No. 1, the "**[***]**" means the [***] used for gene transduction, which is further described in Telethon-HSR's [***]. [***] means [***], including without limitation any patents issuing therefrom, any patent applications and/or issued patents claiming priority thereto, and any reissues, re-examinations, divisionals, continuations, and continuations in part arising therefrom in any jurisdiction"

(C) ***Validation of the [***] Protocol***. Following completion of the Additional GMP Protocol Work, GSK will provide to Telethon-HSR the GMP-suitable protocol developed during the Additional GMP Protocol Work. The JSC will agree upon clinical hypothesis validation work and process validation work that may be necessary to validate the GMP-suitable [***] Protocol, which will include testing and validation (likely through a GLP biodistribution mouse study to be performed with material processed with a GMP-like/pre-GMP protocol reflecting as feasible the procedure that will be used for the clinical protocol.) in preclinical models available to Telethon-HSR. Successful clinical hypothesis validation means that the protocol allows [***] by a biodistribution study similar to that performed for the [***] (the "**Clinical-Hypothesis Validation Studies**"). The validated GMP-suitable [***] Protocol will be transferred to a designated third party CMO for implementation, and Telethon-HSR will collaborate with such designated third party CMO and GSK to transfer the GMP-suitable [***] and to use the GMP-suitable [***] to run GMP batches using donor material for the use in the [***]. Upon the successful completion of the [***] GMP batch run using [***] and the [***] Protocol by such designated third party CMO, Telethon-HSR will earn the "[***]" milestone payment as set forth in the amended Section 6.2 (as amended by this Amendment No. 1). With no prejudice to the provision set out under Clause 2.4(c)(iv)(B) of this Amendment No. 1 in relation to

Additional GMP Protocol Work IP, ownership of any intellectual and industrial property rights related to the GMP Production Protocol, the GMP Clinical Protocol and to the results arising in the conduct of the Clinical-Hypothesis Validation Studies shall be determined and managed in accordance with Clause 8.1 and 8.2 of the Collaboration Agreement; subject however (i) to Clause 4.3 of the Collaboration Agreement (as for the intellectual and industrial property rights in the ownership of Telethon-HSR), (ii) to a non-exclusive license to Telethon-HSR for research purposes (as for the intellectual and industrial property rights in the ownership of GSK) and (iii) to the provisions of Section 12.5(b) in case of termination.

(D) Notwithstanding Section 2.4(c)(iv)(C) above, if JSC agrees that the Additional GMP Protocol Work is sufficiently validated (taking into account data produced by Telethon-OSR) prior to transferring the Additional GMP Protocol Work to Telethon-HSR, the Parties may elect for GSK to transfer the Additional GMP Protocol Work directly to the designated third party CMO. It is however understood that upon successful completion of the [***] GMP batch run using [***], Telethon- OSR will earn the "[***]" milestone payment as set forth in Section 6.2 (as amended by this Amendment No. 1).

3. Amendment of Article 4 of the Collaboration Agreement.

a. Article 4 of the Collaboration Agreement shall be amended to add the following new Clause 4.15:

"4.15 Option rights Granted to GSK for [***].

(a) As of the Amendment No. 1 Effective Date, Telethon-HSR hereby grant to GSK a non-exclusive, worldwide, sublicenseable (subject to Section 4.13) license, in the Territory under all of TELETHON-HSR's and its Affiliates' rights, title and interest in and to [***] as well as the [***] for GSK's Research and Development purposes related to the

Collaboration Programs. Upon GSK's exercise of its Option for the Beta-Thal Program under Section 4.2 (d) of the Collaboration Agreement, the license under the [***] as well as the [***] as set forth herein shall become an exclusive license for use in the Beta-Thal indication and in each of the Collaboration Programs in relation to which GSK may have exercised the option in accordance with the Collaboration Agreement."

4. Amendment of the Development Plan for the Beta-Thal Program Clinical Studies.

a. **Exhibit C** ("Proof of Concept Criteria") shall be deleted in its entirety solely with respect to the Beta-Thal Program and replaced with **Exhibit C-1** "**Beta-Thal Program Proof of Concept Criteria**", attached to this Amendment No. 1 and incorporated herein by reference.

b. The Development Plan for the Beta-Thal Program shall be amended to:

i. Increase the total number of patients to be included in the [***] (defined below) study for the Beta-Thal Program from [***] in the current Development Plan to a total of up to [***] patients. The [***] patients to be treated into the Beta-Thal Program will consist of [***] and [***]. "**[***]**" as used in this Amendment No. 1 are defined to be patients under the age of [***] of age; and

ii. Include a further sub-set of [***] patients to be treated by the [***], provided the Beta-Thal Program has exceeded the scientific Futility analysis conducted by GSK (as set forth below) and GSK has therefore elected to continue the Beta-Thal Program; and Telethon-HSR shall conduct the PoC Study for the Beta-Thal Program in accordance with the amended Development Plan.

c. Patients treated in the Beta-Thal Program without use of the [***] shall be referred to in this Amendment No.1 as being treated by the [***] (the "**[***]**"). The [***] cohort of patients for the initial [***] study shall consist of a total of [***] patients.

d. **Futility Analysis**. Telethon-HSR shall inform GSK in writing when [***] patients have each been treated in the Beta-Thal Program using the [***] (and regardless of whether any [***] patients have also been treated) for a period of at least [***] as measured from the date of treatment with transduced cells, and shall provide to GSK a data package containing the data collected by Telethon-HSR with respect to such patients (the "**Futility Data Package**". Once GSK receives the Futility Data Package, GSK will review the data and determine whether the Beta-Thal Program using the [***] is scientifically Futile. For purposes of this Amendment, scientifically

"**Futile**" means that none of the [***] patients show at least a [***] reduction in [***] in the [***] period from the [***] to the [***] (inclusive) after treatment with transduced cells as compared to such [***] of such patient prior to treatment in the clinical study. In contrast, the study will not be viewed as scientifically Futile if at least [***] of the first [***] patients shows at least a [***] reduction in [***]. GSK will make a determination of whether the Beta-Thal Program using the [***] is scientifically Futile within [***] after receipt of the Futility Data Package (the "**Futility Review Period**") and will communicate such decision to Telethon-HSR in writing, including GSK's decision regarding whether GSK elects to terminate the Beta-Thal Program as set forth in Section 5 of Amendment No.1, or to continue the Beta-Thal Program (regardless of the Futility determination). Telethon-HSR will not dose the first patient in the [***] prior to receipt by GSK of GSK's decision whether to terminate the Beta-Thal Program based on Futility. If GSK terminates the Beta-Thal Program following the determination of scientific Futility, then the Beta-Thal Program (including the [***]), shall be deemed to be a Telethon-HSR Development Program and the terms set forth in Section 4.9 of the Collaboration Agreement shall apply. In derogation to the terms set forth in Section 5.2 of the Collaboration Agreement, the licenses granted in Clause 2.4(c)(iv)(B) of this Amendment No.1 exclusively related to the Additional GMP Protocol Work IP shall survive as non-exclusive licenses for each Collaboration Program for which GSK elects not to exercise its Option and as exclusive license for such Collaboration Programs for which GSK has exercised the Option prior to such termination. It is understood that if following termination of the Beta-Thal Program based on Futility GSK requests to access, for any Collaboration Programs, validated data obtained through the GLP biodistribution data performed by Telethon-HSR following such termination, Telethon-HSR will be entitled to be paid the "[***]" milestone payment as set forth in Section 6.2 (as amended by this Amendment No. 1).

e. If the Beta-Thal Program is determined to meet the Futility analysis conducted by GSK and GSK therefore elects to continue the Beta-Thal Program, Telethon-HSR shall use its Commercially Reasonable Efforts to proceed to enroll and treat a total of [***] patients using the [***].

f. Prior to initiating treatment of a patient under the [***] or under the [***] for Beta-Thal Program clinical studies, as applicable, Telethon-HSR shall ensure that each such patient has executed appropriate informed consent forms. Upon the earliest opportunity to amend the protocol for the study for the purpose of updating the informed consent forms, Telethon-HSR shall amend such informed consent forms to include the language attached hereto as **Exhibit E**, and will re-consent the study patients under informed consent forms that include the **Exhibit E** language. It is understood that upon the Amendment no. 1 Effective Date the language under Exhibit E is under evaluation by the Ethical Committee and, thus, susceptible of possible changes which in no case may entail any liability upon Telethon-HSR.

g. For a period of [***] years post-treatment of each patient treated in the Beta-Thal PoC Study, Telethon-HSR shall conduct all required follow-up activities for each such patient. Telethon-HSR's obligation to conduct such follow-up activities for each patient for the [***] period post-treatment shall apply regardless of whether or not GSK elects to exercise its Option to the Beta-Thal Program. If, at the time GSK exercises its Option to the Beta-Thal Program, additional follow-up (beyond the initial [***] period) is required for any patient treated in the Beta-Thal PoC Study, then GSK will be responsible for such follow-up for such patient(s). If additional follow-up (beyond the initial two-year period) is required with respect to a patient treated in the Beta-Thal PoC Study prior to the exercise by GSK of its Option for the Beta-Thal Program, Telethon-HSR will continue to conduct such follow-up activities for such patient and GSK will reimburse Telethon-HSR for the costs for such additional required follow-up activities for such patient(s).

5. Amendment of Clause 4.2(d)(i) ("Exercise of Option") in the Collaboration Agreement. Clause 4.2(d)(i) ("Exercise of Option") in the Collaboration Agreement shall be deleted in its entirety solely with respect to the Beta-Thal Program and replaced with the following for the Beta-Thal Program:

"4.2(d)(i) *Exercise of Option.*

(A) The "**Option Period Start**" with respect to the Beta-Thal Program will commence upon:

a. the receipt by GSK of the Milestone Report for the Proof of Concept Study; or

b. GSK's right to exercise its Option early arising in accordance with Clause 4.2(d)(ii) of the Collaboration Agreement or Clause 4.8(a) of the Collaboration Agreement, or Clause 12.5(c) of the Collaboration Agreement; or

c. as otherwise agreed by the Parties in writing.

(B) TELETHON-HSR will, in order to enable GSK to determine whether or not to exercise the Option, provide access to the TELETHON-HSR data room containing the set of materials and clinical and preclinical information related to the Beta-Thal Program, including such materials and information related to the [***] and if available the [***] studies.

(C) GSK shall decide whether or not to exercise the Option and may exercise the Option with respect to the Beta-Thal Program by written notice to TELETHON-HSR at any time during the Review Period (defined below), unless extended by the mutual written agreement of the Parties. Upon GSK's exercise of an Option and receipt by TELETHON-HSR of the applicable Option Exercise Fee set forth in Section 4.2(d)(iii) of Amendment No. 1, the Beta-Thal Program will become a GSK Development Program.

(D) With respect to the Beta-Thal Program, the "**Review Period**" during which GSK may exercise its Option shall commence on the date of the Option Period Start and will continue until [***] following the treatment of the [***] patient in the Beta-Thal Program, provided that:

a. the Milestone Report must include the Proof of Concept data package demonstrating the Proof of Concept criteria as set forth in Exhibit C-1 of the Amendment No. 1 for any [***] patients treated in the [***] with a minimum of [***] years of post-treatment follow-up data; provided that all [***] patients from the [***] cohort have been also treated in the PoC Study; and

b. at least [***] patient from the [***] cohort has been followed up for at least [***] post treatment.

In the event that Telethon-HSR is unable to provide a Proof of Concept package demonstrating the Proof of Concept criteria as set forth in Exhibit C-1 of the Amendment No. 1 for any [***] patients treated in the [***] with a minimum of [***] years of post-treatment follow-up data as set forth in Clause 4.2(d)(i)(D)(a) of the Collaboration Agreement, then the Review Period will extend until [***] after Telethon-HSR provides a Milestone Report that includes the complete Proof of Concept package demonstrating the Proof of Concept criteria as set forth in Exhibit C-1 of the Amendment No. 1 for a total of any [***] patients treated under the [***] and/or the [***], with a minimum of [***] of post-treatment follow-up data.

(E) Data and results of patients treated by the [***] shall be deemed to be included in, and part of, the Beta-Thal Program and shall be provided to GSK and automatically included in GSK's Option for the Beta-Thal Program.

(F) Subject to Section 5.3(b) of the Collaboration Agreement, any Option exercise with respect to the Beta-Thal Program shall be irrevocable."

6. Milestones and Royalties; Payments.

a. Amendment of Clause 6.1 (Upfront Payment) of the Collaboration Agreement.

i. Clause 6.1 of the Collaboration Agreement shall be amended to add the following:

"GSK shall pay to TELETHON-HSR a non-refundable, non-creditable payment in the amount of [***] (the "**[***]**") within [***] after receipt of an invoice by GSK on or after the Amendment No. 1 Effective Date. Telethon and OSR will each receive half of this amount and therefore be entitled to issue, after the Effective Date, separate invoices (to be paid within [***] after receipt of Invoice) for the amount of [***] each."

b. *Amendment of Clause 6.2* (*Development, Regulatory, and Commercial Milestone Payments*). The column of the Milestone payment chart set forth in Clause 6.2 (b) of the Collaboration Agreement entitled "Lentivirus ß Thalass" shall be deleted in its entirety and replaced with the chart set forth in this Section 6(b) of this Amendment No. 1 below. As of the Amendment No. 1 Effective Date, the milestone events and corresponding milestone payments as set forth in the chart below in this Section 6(b) of Amendment No. 1 shall be the set of sole milestone events and corresponding milestone payments to apply to the Beta-Thal Program. Following achievement of the corresponding milestone event in the Beta-Thal Program, Telethon-HSR shall invoice GSK for the applicable milestone payment and GSK shall make the non-refundable, non-creditable milestone payment to TELETHON-HSR within [***] following receipt of an invoice for such milestone payment. All of the milestones set forth below in this Section 6(b) of this Amendment No. 1 shall be payable only once for the Beta-Thal Program, regardless of the number of times such milestone event may be achieved. For the avoidance of doubt, (i) no bonus milestone payment will be paid by GSK for the "[***]" as set forth in Clause 6.2(b) of the Collaboration Agreement, and (ii), upon Option exercise by GSK for the Beta-Thal Program, such Option exercise shall automatically also include the [***] as part of the Beta-Thal Program without payment of any additional fees or any additional milestone or royalty streams specifically allocated to the [***].

Beta-Thal Program Milestone Events:

Milestone Event	**Lentivirus-ß Thalass Milestone Payment (€ M)**
Pre-Clinical Contingent Bonus Milestone	
[***]	[***]
Development Milestones	
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]
[***]	[***]

Milestone Event	Lentivirus-ß Thalass Milestone Payment (€ M)
[***]	[***]
[***]	[***]
Marketing Authorization Approval Milestones	
[***]	[***]
Sales Milestones	
[***]	[***]
[***]	[***]

**[***]
***[***]
****[***]

c. Clinical PoC Option Exercise Fee. In the event GSK elects to exercise its Option with respect to the Beta-Thal Program in accordance with Section 5 of this Amendment No.1, GSK will inform Telethon-HSR in writing. Telethon HSR shall thereafter invoice GSK for the Option Exercise Fee in the amount of [***] (the "**Beta-Thal Option Exercise Fee**") and GSK shall pay such invoice within [***] after receipt of such invoice by GSK pursuant to Article 6.5 of the Collaboration Agreement.

7. GSK's Right to Terminate the Beta-Thal Program for Scientific Futility. Article 12 ("Termination") of the Collaboration Agreement shall be amended to include the following, which shall apply solely to the Beta-Thal Program:

"Termination by GSK as a result of Scientific Futility. Once [***] non-pediatric patients have each been treated in the Beta-Thal Program using the [***] (and regardless of whether any [***] have also been treated) for a period of at least [***] as measured from the date of treatment with transduced cells, then GSK may evaluate the data and results available for all [***] such [***]. If GSK's scientific review of the then-available data and results show that continuation of the study would be Futile (as defined in section 4(d)), then GSK may elect to terminate this Amendment No. 1 and the Beta-Thal Program immediately by providing written notice of termination to Telethon-HSR. Upon termination of the Beta-Thal Program as a result of Scientific Futility, then GSK shall have no further obligations to pay any future amounts associated with the Beta-Thal Program,

including without limitation, payment of any milestone amounts for achievement of milestone events following termination. Termination of this Amendment No. 1 and of the Beta-Thal Program shall be treated as a termination by GSK for convenience and the terms of Clause 12.5(b) (Effects of Termination) of the Collaboration Program shall apply."

It is understood that in case of termination by GSK as a result of Scientific Futility, the Side Letter Agreements listed in Section 9, will survive the termination.

8. Anti-Bribery, Anti-Corruption.

   a. Each Party acknowledges that it has received and read GSK's 'Prevention of Corruption—Third Party Guidelines' attached hereto as **Exhibit A**, and agrees to perform its obligations under the Collaboration Agreement in accordance with the principles set out therein.

   b. Each Party agrees to comply fully at all times with all applicable laws and regulations, including but not limited to applicable anti-corruption laws, of the territory in which such Party conducts business.

   c. Either Party shall be entitled to terminate this Amendment No.1 or the Collaboration Agreement immediately on written notice to the other Party, if the other Party fails to perform its obligations in accordance with this Section 8 of Amendment No. 1. Neither Party shall have no claim against the other Party for compensation for any loss of whatever nature by virtue of the termination of this Agreement in accordance with this Section 8 of Amendment No. 1. To the extent (and only to the extent) that the laws of the territory provide for any such compensation to be paid to the terminating Party upon the termination of this Amendment No. 1 or the Collaboration Agreement, the non-terminating Party hereby expressly agrees (to the extent possible under the laws of the territory) to waive or to repay to the terminating Party any such compensation or indemnity.

9. Inclusion of Side Letter Agreements. The following side letter agreements (the "Side Letter Agreements") have been entered into between the Parties as of the dates set forth in each respective Side Letter Agreement, and have been incorporated into, and form part of, the terms of the Collaboration Agreement as of the dates set forth in each respective Side Letter Agreement. Termination of the Collaboration Agreement and/or termination under this Amendment No. 1 shall not terminate the Side Letter Agreements, which shall survive in accordance with the terms set forth therein. The Side Letter Agreements entered into as of the Amendment No. 1 Effective Date and which have also been incorporated by reference into the Collaboration Agreement are as follows:

a. *Side Letter No. 1*: 26 June 2012, by and between Glaxo Group Ltd, and Fondazione Telethon, re: Addition of [***] additional patients in the Metachromatic Leukodystrophy Clinical Study (patients [***]);

b. *Side Letter of Nov. 2012*: Nov 2, 2012 by and between GlaxoSmithKline Research and Development Limited, Telethon and Fondazione Centro San Raffaele, re: Beta- Thal Program and MPS-1 Program pre-clinical support.

c. *Side Letter No. 2*: 11 June 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Expansion of GLP Facilities;

d. *Side Letter No. 3*: 28 June 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: [***];

e. *Side Letter No. 4*: 04 September 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Extension of Option Exercise Period for MLD Program;

f. *Side Letter No. 5*: 27 November 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Further Extension of Option Exercise Period for MLD Program;

g. *Side Letter No. 6*: 30 August 2014, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for MLD patients [***] for treatment of such patients following GSK option exercise and prior to GSK's execution of agreements with MolMed to cover such costs; and

h. *Side Letter No. 7*: 30 August 2014, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for WAS patients [***] for treatment of such patients following GSK option exercise and prior to GSK's execution of agreements with MolMed to cover such costs.

i. *Side letter No. 8*: 9 February 2015, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments and or back up costs for MLD patients:[***].

j. *Side letter No. 9*: 9 February 2015, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for WAS additional patient.

10. Extension of Research Term. Article 2.3 (Research Term) of the Collaboration Agreement shall be deleted in its entirety and replaced with the following:

"The Research term shall commence on the Effective Date and shall expire, on a Program-by-Program basis, upon the earlier of (i) eight (8) years after the Effective Date, or (ii) the date that the last Option with respect to any Collaboration Program is exercised or expires un-exercised by GSK (unless terminated earlier in accordance with this Agreement) (the "**Research Term**"), subject to extension if mutually agreed in writing by the Parties."

11. Miscellaneous. In the event of a conflict of terms between this Amendment No. 1 and the Collaboration Agreement, the terms of this Amendment No. 1 shall control. Except as expressly amended by this Amendment No. 1 or the Side Letter Agreements included in this Amendment No.1, the Collaboration Agreement shall remain in full force and effect according to its terms. This Amendment No. 1 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 1 will be legal and binding on both Parties. This Amendment No. 1 shall be incorporated into and shall, as of the Amendment No. 1 Effective Date, form part of the Collaboration Agreement between the Parties.

*_*_*_*_*_*_*_*_*_*_*_*_*

[Signatures Follow on Next Page]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 1 to be executed by their duly authorized representatives as of the Amendment No. 1 Effective Date.

For TELETHON-HSR:

Fondazione Telethon

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

EXHIBIT A

PREVENTION OF CORRUPTION—THIRD PARTY GUIDELINES

The GSK Anti-Bribery and Corruption Policy (POL-GSK-007) requires compliance with the highest ethical standards and all anti-corruption laws applicable in the countries in which GSK (whether through a third party or otherwise) conducts business. POL-GSK-007 requires all GSK employees and any third party acting for or on behalf of GSK to ensure that all dealings with third parties, both in the private and government sectors, are carried out in compliance with all relevant laws and regulations and with the standards of integrity required for all GSK business. GSK values integrity and transparency and has zero tolerance for corrupt activities of any kind, whether committed by GSK employees, officers, or third-parties acting for or on behalf of the GSK.

Corrupt Payments - GSK employees and any third party acting for or on behalf of GSK, shall not, directly or indirectly, promise, authorise, ratify or offer to make or make any “payments” of “anything of value” (as defined in the glossary section) to any individual (or at the request of any individual) including a “government official” (as defined in the glossary section) for the improper purpose of influencing or inducing or as a reward for any act, omission or decision to secure an improper advantage or to improperly assist the company in obtaining or retaining business.

Government Officials - Although GSK’s policy prohibits payments by GSK or third parties acting for or on its behalf to any individual, private or public, as a “quid pro quo” for business, due to the existence of specific anticorruption laws in the countries where we operate, this policy is particularly applicable to “payments” of “anything of value” (as defined in the glossary section), or at the request of, “government officials” (as defined in the glossary section).

Facilitating Payments - For the avoidance of doubt, facilitating payments (otherwise known as “greasing payments” and defined as payments to an individual to secure or expedite the performance of a routine government action by government officials) are no exception to the general rule and therefore prohibited.

GLOSSARY

The terms defined herein should be construed broadly to give effect to the letter and spirit of the ABAC Policy. GSK is committed to the highest ethical standards of business dealings and any acts that create the appearance of promising, offering, giving or authorising payments prohibited by this policy will not be tolerated.

Anything of Value: this term includes cash or cash equivalents, gifts, services, employment offers, loans, travel expenses, entertainment, political contributions, charitable donations, subsidies, per diem payments, sponsorships, honoraria or provision of any other asset, even if nominal in value.

Payments: this term refers to and includes any direct or indirect offers to pay, promises to pay, authorisations of or payments of anything of value.

Government Official shall mean:

- Any officer or employee of a government or any department, agency or instrument of a government;
- Any person acting in an official capacity for or on behalf of a government or any department, agency, or instrument of a government;
- Any officer or employee of a company or business owned in whole or part by a government;
- Any officer or employee of a public international organisation such as the World Bank or United Nations;
- Any officer or employee of a political patty or any person acting in an official capacity on behalf of a political party; and/or
- Any candidate for political office.

EXHIBIT B

Description of Preclinical Mouse Study to be conducted by Telethon -HSR

While the GMP production protocol is being developed, Telethon-OSR will continue to pursue exploratory studies in order to ensure rapid implementation of the GMP Clinical Protocol.

These studies will comprise

1. [***]
2. [***]
3. [***]

Exhibit C-1 "Beta-Thal Program Proof of Concept Criteria

PoC Study for Beta Thalassimia:

Minimum Years of Follow up post-treatment: [***]

Primary End-points

Safety (applicable to all patients treated)

1) **Overall survival**
2) **Achievement of hematological engraftment** [***].
3) **Safety of the administration of autologous HSC transduced with LV-GLOBE**. [***].
4) **Short-term safety and tolerability of the different conditioning regimens**. [***]
5) **Overall safety** and **tolerability** [***].
6) **Polyclonal engraftment and absence of clonal dominance** (**as defined per clinical trial protocol**) [***].
7) **Absence of oncogenesis related to ATIMP injection**

Efficacy

1) **Reduction in transfusion frequency up to transfusion independence in any** [***] **patients with data for at least** [***] **post-ATIMP**.

Secondary End-points

Efficacy

1) Transfusion independence at [***] from ATIMP injection.
2) Adequate Hb level [***] of follow-up in patients who reach transfusion independence.
3) Adequate engraftment of genetically corrected cells [***].
4) Presence [***] of transgene expression or at least [***] increase [***] of transgene expression at [***] from ATIMP injection.
5) Improvement of health-related quality of life (HRQoL) at [***] of follow-up compared to baseline.

Absence of unfavourable Risk/Benefit ratio leading to study termination as assessed by the Principal Investigator or independent Data Safety Monitoring Board.

Exhibit D

Beta thalassemia Program Development Plan Summary—as of February 2015.

This plan increases the number of patients from whom data would be available at PoC from [***] patients with [***] of follow up to [***] patients, providing a more appropriate data set for decision making for this disease which affects a larger population with a wide age range and for which standard of care prolongs life expectancy. This plan includes paediatric patients and treatment using the "[***]" process which may [***] and lead to [***].

The initial [***] allows for treatment of [***] patients, comprising [***] and [***] using the [***].

In addition, the parties plan to activate an improvement project referred to as the [***]. Subject to successful completion of pre-clinical work to develop a GMP Protocol, and subject to approval from appropriate ethical committees and regulatory authorities, the intention is to treat [***] patients in a clinical research protocol using the [***].

Whilst the timing of the different elements of the plan is not certain, the projection is that [***] data on [***] in the TIGET-BTHAL Protocol will be available around the [***], and this will be the earliest opportunity to deliver PoC package. At that date, it is planned that there will be data on up to [***] from the [***] protocol, including at least [***] data on [***] from that Protocol.

[***]

EXHIBIT E

TIGET Proposed ADDITIONAL Paragraph for Beta Thal Informed Consent Form:

omissis

1. [***]

2. [***]

3. [***]

Proposed Additional Declaration of Consent:

[***]

AMENDMENT NO. 2 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 2 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 2**") is entered into as of this 4th day of April 2016 (the "**Amendment No. 2 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline Intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 2 amends that certain Research and Development Collaboration and License Agreement entered into on October 15, 2010 between GGL, Telethon and Fondazione Centro San Raffaele del Monte Tabor, as amended by Amendment No. 1 on 31 March 2015 (the "**Amendment No. 1**") (the agreement, as amended by Amendment No. 1, the "**Collaboration Agreement**"). Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "Party" and collectively as the "Parties." Telethon and OSR may be referred to herein collectively as "Telethon-HSR".

WHEREAS, the Parties are collaborating on several Collaboration Programs for *ex vivo* hematopoietic stem cell gene therapy of monogenic diseases, including a Collaboration Program in Beta-thalassemia (the "**Beta-Thal Program**");

WHEREAS, certain costs and expenses related to the conduct of the Beta-Thal Program [***] and the Parties have agreed to re-allocate a portion of the Option Fee for the Beta-Thal Program to an earlier milestone payment and have agreed upon a certain cost-sharing arrangement [***] for the Beta-Thal Program; and

WHEREAS, the Parties now desire to enter into this Amendment No. 2 to capture their agreement with respect to the above referenced subject matters, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1. Amendment of Milestone Payment and Option Fee. Clause 6(b) of the Amendment No. 1 shall be amended, solely with respect to the Beta-Thal Program, to amend the "[***]" milestone as set forth therein and in Amendment No.1 to increase such milestone payment from [***] to [***]. Correspondingly, the Beta-Thal Option Exercise Fee is reduced from [***] down to [***] (the "**Beta-Thal Option Exercise Fee**").

2. Payment for Additional Beta-Thal Lentiviral Vector Batches. As of this Amendment No. 2 Effective Date, the agreed-upon development plan for the Beta-Thal Program includes a total of [***] batches of lentiviral vector for the development activities to be conducted by Telethon-HSR for the Beta-Thal Program. [***]. In the event

that Telethon-HSR determines that additional batches of lentiviral vector (i.e. more than [***]) are needed to conduct the Beta-Thal Program clinical studies through to the conclusion of the [***] Study, Telethon-HSR will notify GSK in writing via the JSC and the Parties will discuss and agree upon the timing and number of additional lentiviral vector to be ordered for the Beta-Thal Program. If the Parties agree that additional batches of vector are needed, then Telethon-HSR will be responsible for the order and payment of any such additional agreed-upon lentiviral vector batches for the Beta-Thal Program. GSK will reimburse Telethon-HSR for the costs of each such agreed upon additional lentiviral vector batch at a rate of [***] per batch, as follows: Telethon-HSR will invoice GSK for the costs of such additional lentiviral vector batch following payment of such batch by Telethon-HSR. GSK will pay such invoiced amount within the first [***] of the month that is [***] following receipt of such invoice by Telethon-HSR. GSK will thereafter deduct [***] of such amounts paid by GSK (the "Telethon-HSR portion") from future royalty payments due from GSK to Telethon-HSR for the Beta-Thal Program, such amounts to be deducted from each future royalty payment until the total Telethon-HSR portion has been exhausted. For the avoidance of doubt, in the event that the Option is not exercised by GSK with respect to the Beta-Thal Program, GSK shall not be entitled to request Telethon-OSR to refund the Telethon-HSR portion.

3. Inclusion of Side Letter Agreements. Clause 9 of the Amendment n.1 shall be amended solely by adding side letter n.10. The Side Letter Agreements entered into as of the Amendment No. 2 Effective Date and which have also been incorporated by reference into the Collaboration Agreement are as follows:

a. *Side Letter No. 1*: 26 June 2012, by and between Glaxo Group Ltd, and Fondazione Telethon, re: Addition of [***] additional patients in the Metachromatic Leukodystrophy Clinical Study (patients [***]);

b. *Side Letter of Nov. 2012*: Nov 2, 2012 by and between GlaxoSmithKline Research and Development Limited, Telethon and Fondazione Centro San Raffaele, re: Beta-Thal Program and MPS-l Program pre-clinical support.

c. *Side Letter No. 2*: 11 June 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Expansion of GLP Facilities;

d. *Side Letter No. 3*: 28 June 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: [***];

e. *Side Letter No. 4*: 04 September 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Extension of Option Exercise Period for MLD Program;

f. *Side Letter No. 5*: 27 November 2013, by and between Glaxo Group Ltd, Ospedale San Raffaele Srl, and Fondazione Telethon, re: Further Extension of Option Exercise Period for MLD Program;

g. *Side Letter No. 6*: 30 August 2014, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for MLD patients [***] for treatment of such patients following GSK option exercise and prior to GSK's execution of agreements with MolMed to cover such costs; and

h. *Side Letter No. 7*: 30 August 2014, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for WAS patients [***] and WAS1008 for treatment of such patients following GSK option exercise and prior to GSK's execution of agreements with MolMed to cover such costs.

i. *Side letter No. 8*: 9 February 2015, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments and or back up costs for MLD patients: [***].

j. *Side letter No. 9*: 9 February 2015, by and between GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd), Ospedale San Raffaele Srl, and Fondazione Telethon, re: Reimbursement of vector production batches and cell processing treatments costs for WAS additional patient.

k. *Side letter No. 10*: 11 December 2015, by GlaxoSmithKline Research and Development Limited (an Affiliate of Glaxo Group Ltd)and between Fondazione Telethon and re: Reimbursement of the 13th vector production batch for the Beta-Thal Program.

4. Miscellaneous. In the event of a conflict of terms between this Amendment No. 2 and the Collaboration Agreement, the terms of this Amendment No. 2 shall control. Except as expressly amended by this Amendment No. 2 or the Side Letter Agreements included in this Amendment No.2, the Collaboration Agreement shall remain in full force and effect according to its terms. This Amendment No. 2 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 2 will be legal and binding on both Parties. This Amendment No. 2 shall be incorporated into and shall, as of the Amendment No. 2 Effective Date, form part of the Collaboration Agreement between the Parties.

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[Signatures Follow on Next Page]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 1 to be executed by their duly authorized representatives as of the Amendment No. 1 Effective Date.

For TELETHON-HSR:

For Fondazione Telethon:

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

AMENDMENT TO
"AMENDMENT NO. 2 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT"

This AMENDMENT TO THE "AMENDMENT NO. 2 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT" (the "**Amendment No. 2bis**") is entered into as of the 17th day of July 2018 (the "**Amendment No. 2bis Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and Orchard Therapeutics Limited ("**OTL**") to which the Research and Development Collaboration and License Agreement dated 15 October 2010 (as subsequently amended; "**Collaboration Agreement**") between Ospedale San Raffaele S.r.l., Fondazione Telethon and Glaxo Group Limited has been novated on 11 April 2018.

This Amendment No. 2bis amends such Amendment No. 2 dated 4 April 2016 (the "**Amendment No. 2**").

Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement.

Each of OTL, Telethon, and OSR may be referred to herein as a "**Party**" and collectively as the "**Parties**". Telethon and OSR may be referred to herein collectively as "**Telethon-OSR**".

WHEREAS, the option right granted in accordance with the Collaboration Agreement in relation to the Beta-Thal Collaboration Program has been exercised on 20 April 2017;

WHEREAS, pursuant to Sections 2.4(a)(i) and 2.4(c)(iii) of the Collaboration Agreement, following to such option exercise all costs and expenses related to the Beta-Thal Collaboration Program shall be supported by OTL;

WHEREAS, notwithstanding the said exercise of the option, Telethon-OSR shall still be responsible to order and pay (in accordance with the terms and conditions set forth under Section 2 of Amendment No. 2) [***] according to the Development Plan of the Beta Thal Program

WHEREAS, to facilitate the process in view of the treatment of [***], the Parties have agreed to increase [***], according to the terms and conditions set forth herein, such that the order shall be for [***];

WHEREAS, the Parties therefore desire to enter into this Amendment No. 2bis to capture their agreement with respect to the above referenced subject matters, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1. The Parties hereby agree that [***] ([***]; hereinafter each the "**[***]**" and collectively the "**[***]**") [***] are needed to [***] within the Beta-Thal Program, each such [***] cost being equal to [***] ([***]); provided, that Telethon-OSR will be responsible for [***] and payment of such [***] for the Beta-Thal Program as follows:

i. according to the arrangements achieved by the Parties with [***]:

a) Telethon-OSR shall pay to [***] an amount equal to [***] ([***]) per [***] ("**Telethon-OSR Payment**");

b) OTL shall pay to [***], an amount equal to [***] ([***]) per [***];

ii. OTL will reimburse Telethon-OSR for the Telethon-OSR Payment for each [***], as follows:

a) Telethon-OSR will invoice OTL for the Telethon-OSR Payment for each [***]; OTL will pay such invoiced amount within the [***] of the month that is [***] following receipt of such invoice issued by Telethon—OSR;

b) OTL will thereafter deduct an amount equal to [***] ([***]) of the cost of [***] needed for [***] from future royalty payments due from OTL to Telethon-OSR for the Beta-Thal Collaboration Program, such amounts to be deducted from each future royalty payment until the total amount mentioned in this Section 1.ii.b) has been exhausted. If [***], and OTL and Telethon-OSR agreed to [***], an incremental similar discount would apply so that in all and any cases, OTL would [***] incurred for [***].

For the avoidance of doubt, unless otherwise agreed in writing by the Parties, OTL shall be responsible to order and pay any [***] required for the development of the Beta-Thal Collaboration Program in accordance with the Collaboration Agreement (this Amendment No. 2bis constituting a derogation to the terms and conditions set forth under the Collaboration Agreement with respect to the Parties' responsibilities after Option exercise).

2. In the event of a conflict of terms between this Amendment No. 2bis and the Amendment No. 2, the terms of this Amendment No. 2bis shall prevail. Except as expressly amended by this Amendment No. 2bis, the Collaboration Agreement shall remain in full force and effect according to its terms. This Amendment No. 2bis may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 2bis will be legal and binding on both Parties. This Amendment No. 2bis shall be incorporated into and shall, as of the Amendment No. 2bis Effective Date, form part of the Collaboration Agreement between the Parties.

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[Signatures Follow on Next Page]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 2bis to be executed by their duly authorized representatives as of the Amendment No. 2bis Effective Date.

For TELETHON-OSR:

Fondazione Telethon

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

Orchard Therapeutics Limited

By: [***]

Name: [***]

Title: [***]

AMENDMENT NO. 3 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 3 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 3**") is entered into as of the 23rd day of September 2016 (the "**Amendment No. 3 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline Intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 3 amends that certain Research and Development Collaboration and License Agreement entered into on October 15, 2010 between GGL, Telethon, Fondazione Centro San Raffaele del Monte Tabor, as amended by Amendment No. 1 on 31 March 2015 (the "**Amendment No. 1**"), and Amendment No. 2 on 4 April 2016 (the "**Amendment No. 2**") (the agreement, as amended by Amendment No. 1 and Amendment No. 2, the "**Collaboration Agreement**"). Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "Party" and collectively as the "Parties". Telethon and OSR may be referred to herein collectively as "Telethon-HSR".

WHEREAS, the Parties are collaborating on several Collaboration Programs for *ex vivo* hematopoietic stem cell gene therapy of monogenic diseases, including a Collaboration Program in Beta-thalassemia (the "**Beta-Thal Program**");

WHEREAS, the Parties have decided to seek [***] regarding certain aspects of the Beta-Thal Program, and the Parties have agreed to re-allocate a portion of the Option Exercise Fee for the Beta-Thal Program as an earlier milestone payment and have agreed that GSK will cover certain additional costs related to [***]; and

WHEREAS, the Parties now desire to enter into this Amendment No. 3 to capture their agreement with respect to the above referenced subject matters, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1 Amendment of Beta-Thal Option Exercise Fee. The Beta-Thal Option Exercise Fee shall be amended to reduce the Beta-Thal Option Exercise Fee from [***] as set forth in the Amendment No. 1 to [***]. GSK will pay such Beta-Thal Option Exercise Fee, as amended under this Section 1, in accordance with the terms set forth in Clause 6.5 of the Collaboration Agreement.

2 Milestone upon [***]. The Collaboration Agreement shall be amended, solely with respect to the Beta-Thal Program, to include an additional milestone event and corresponding milestone payment of [***] to be achieved upon [***]. Telethon-OSR may invoice GSK for such milestone payment upon achievement of the milestone event, and GSK will pay such invoiced amount in accordance with the terms set forth in Clause 6.5 of the Collaboration Agreement; provided that solely with respect to the milestone payment set forth in this Section 2, in derogation to such Clause 6.5, the payment terms shall be reduced to [***] after receipt by GSK of the invoice from Telethon-OSR.

3 The Parties have also agreed that GSK shall reimburse Telethon for fees incurred by Telethon in connection with [***], of [***]. Telethon shall invoice GSK for such fees, including proof of payment by Telethon of the same, and GSK will reimburse such amounts within [***] after receipt by GSK of the invoice issued by Telethon.

4 Miscellaneous. In the event of a conflict of terms between this Amendment No. 3 and the Collaboration Agreement, the terms of this Amendment No. 3 shall control. Except as expressly amended by this Amendment No. 3, the Collaboration Agreement (including all of the Side Letter Agreements incorporated therein) shall remain in full force and effect according to its terms. This Amendment No. 3 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 3 will be legal and binding on all Parties. This Amendment No. 3 shall be incorporated not and shall, as of the Amendment No. 3 Effective Date, form part of the Collaboration Agreement between the Parties.

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[*Signatures Follow on Next Page*]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Par ties have caused this Amendment No. 3 to be executed by their duly authorized representatives as of Amendment No. 3 Effective Date.

For Fondazione Telethon:

By: [***]
Name: [***]
Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

AMENDMENT NO. 4 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 4 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 4**") is entered into as of the 15th day of December 2016 (the "**Amendment No. 4 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline Intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 4 amends that certain Research and Development Collaboration and License Agreement entered into on October 15, 2010 between GGL, Telethon, Fondazione Centro San Raffaele del Monte Tabor, as amended by Amendment No. 1 on 31 March 2015 (the "**Amendment No. 1**"), and Amendment No. 2 on 4 April 2016 (the "**Amendment No. 2**"), and Amendment No. 3 on 23rd day of September 2016 (the "**Amendment No. 3**") (the agreement, as amended by Amendments No. 1, No. 2, and No. 3 the "**Collaboration Agreement**"). Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "Party" and collectively as the "Parties". Telethon and OSR may be referred to herein collectively as "Telethon-OSR".

WHEREAS, GSK exclusively licensed the ex-vivo gene therapy program for ADA-SCID under the terms of the Collaboration Agreement and obtained approval from the EMA to commercialize such gene therapy medicine for ADA-SCID on 27 May 2016;

WHEREAS, as of the Amendment No. 4 Effective Date, Ospedale San Raffaele is the only approved treatment centre to provide the ex-vivo gene therapy treatment for ADA-SCID (marketed by GSK under the name Strimvelis™); and

WHEREAS, providing this treatment at a single treatment centre requires additional activities and additional at-risk investments by Telethon that were not contemplated under the original Collaboration Agreement, but which have been determined by the Parties to be critical to commercial success of Strimvelis™; and

WHEREAS, Telethon created, at its sole risk, [***] to support, as may be needed, patients and their family, in the form of a package of services which may include [***], as determined in the reasonable judgement of Telethon-; and

WHEREAS, the Parties now desire to enter into this Amendment No. 4 to capture their agreement with respect to the above referenced subject matters, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1. Amendment of Clause 6.2 of the Agreement. Clause 6.2(a) of the Agreement (Development, Regulatory and Commercial Milestones) shall be amended, solely as such clause applies to the ADA-SCID Collaboration Program, to include the following additional milestone payment for the ADA-SCID Collaboration Program milestone payments as set out in the table in Clause 6.2(b) of the Agreement. The Parties agree that the [***] milestone payment shall be paid solely to Telethon, in recognition that as between OSR and Telethon, Telethon has created [***] and has availed and is willing to avail of such [***].

Milestone Events	Programs M £						
	Retrovirus ADA-SCID	Lentivirus WAS	Lentivirus MLD	Lentivirus ß Thalass	Lentivirus MPS	Lentivirus GLD	Lentivirus CGD
[***]	[***]	[***]	[***]	[***]	[***]	[***]	[***]

* Solely for purposes of this milestone payment for the ADA-SCID Collaboration Program:

- [***]
- [***]

2. Telethon will use its Commercially Reasonable Efforts to provide patient support services up to the first [***] Patients (as defined above) treated at OSR with the Strimvelis™ gene therapy medicine.

3. Miscellaneous. In the event of a conflict of terms between this Amendment No. 4 and the Collaboration Agreement, the terms of this Amendment No. 4 shall control. Except as expressly amended by this Amendment No. 4, the Collaboration Agreement (including all of the Side Letter Agreements incorporated therein) shall remain in full force and effect according to its terms. This Amendment No. 4 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 4 will be legal and binding on all Parties. This Amendment No. 4 shall be incorporated not and shall, as of the Amendment No. 4 Effective Date, form part of the Collaboration Agreement between the Parties.

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[*Signatures Follow on Next Page*]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 4 to be executed by their duly authorized representatives as of the Amendment No. 4 Effective Date.

For Fondazione Telethon:

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

AMENDMENT NO. 5 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 5 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 5**") is entered into as of the 15th day of July 2017 (the "**Amendment No. 5 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 5 amends that certain Research and Development Collaboration and License Agreement entered into on October 15, 2010 between GGL, Telethon, Fondazione Centro San Raffaele del Monte Tabor, as amended by Amendment No. 1 on 31 March 2015 (the "**Amendment No. 1**"), and Amendment No. 2 on 4 April 2016 (the "**Amendment No. 2**"), and Amendment No. 3 on 23rd day of September 2016 (the "**Amendment No. 3**"), and Amendment No. 4 on 15 December 2016 (the "**Amendment No. 4**") (the agreement, as amended by Amendments No. 1, No. 2, No. 3, and No. 4 the "**Collaboration Agreement**"). Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "Party" and collectively as the "Parties". Telethon and OSR may be referred to herein collectively as "Telethon-OSR".

WHEREAS, GSK has provided notice of its Option exercise for the Beta-Thalassemia Collaboration Program (the "**B-Thal Program**") under the terms of the Collaboration Agreement;

WHEREAS, as the B-Thal program has progressed, the teams have received [***];

WHEREAS, the Parties have agreed to clarify and amend the Agreement with respect to certain provisions relating to the B-Thal Collaboration Program; and

WHEREAS, the Parties now desire to enter into this Amendment No. 5 to formalize their agreement with respect to the above referenced subject matter, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1 Conduct of activities for a [***].

a. *General.* Within [***] following the Amendment No. 5 Effective Date, Telethon-OSR and GSK will discuss in good faith and agree upon a development plan for the conduct of activities up to the completion of a Proof-of-Concept Study for the [***] using [***] (together with the [***] vector, the "**Licensed Vectors**"), including the respective activities and responsibilities allocated to each Party ("**[***] Plan**"). For clarity, GSK's obligations under Section 5.1(c) of the Collaboration Agreement with respect to the B-Thal Program shall be satisfied by the Beta-Thalassemia indication and shall not be construed to include additional diligence obligations for a [***] in the B-Thal Program. GSK's license grant to the B-Thal Program shall remain in full force and effect so long as GSK is pursuing at least [***] indication in the B-Thal Program as required in Section 5.1(c) of the Collaboration Agreement.

b. The [***] shall include

(a) *Pre-clinical Activities; Research Support Payments.* GSK and Telethon-OSR will agree upon the specific non-CMC pre-clinical activities to be conducted by Telethon-OSR according to the [***], including a budget for such activities and an annual and overall cap for the costs for such activities. The annual budget for work to be conducted by Telethon-OSR shall be divided into equal quarterly payments (each quarterly payment, a "**Research Payment**" and collectively, the "**Research Payments**"). Telethon-OSR and GSK agree that Research Payments shall be a reasonable fair market value, taking into account administrative overhead costs. Following agreement on the pre-clinical research plan (including the approved budget) for the [***], Telethon-OSR will invoice GSK for the first quarterly Research Payment and GSK will pay such invoiced amount within [***] of receipt of invoice by GSK. Telethon-OSR will thereafter invoice GSK for each subsequent quarterly Research Payment to be made by GSK under the [***] Plan for pre-clinical activities at least [***] prior to the first day of each calendar quarter, and GSK shall pay such quarterly payments on the [***], provided that GSK shall not be obligated to make any such quarterly Research Payments less than [***] after receipt by GSK of the relevant invoice from Telethon-OSR. Both Parties declare that they have adopted model anti-bribery/anti-corruption practices according to Italian law 231/01. GSK will be responsible for the CMC work and for all other aspects eventually needed for manufacturing with respect to the [***].

(b) *Proof-of-Concept Study.* The Parties currently anticipate that a clinical PoC Study ([***]) will be required to support an MAA file in order to obtain a [***] for the B-Thal product (if approved). GSK and Telethon-OSR will work together in good faith to agree upon the protocol and clinical trial design for a [***], including a study budget for the conduct of the PoC Study (the "**[***] Study**"). [***].

(c) *Multicentre Confirmatory Study.* GSK will be responsible for the multicentre confirmatory study and for all other aspects eventually needed for commercialization of a GSK Product with respect to the [***].

2 Amendment of Section 3 (Management of the Collaboration). Solely with respect to the B-Thal Collaboration Program, Section 3.1(c) of the Collaboration Agreement shall be amended to include the following statement. This amended Section 3.1(c) shall not apply to any other Collaboration Program under the Collaboration Agreement.

"Solely with respect to the B-Thal Program, following GSK's Option exercise, the Joint Steering Committee shall continue to oversee the pre-clinical and clinical Development activities (up to the completion of a PoC Study) for the Development Licensed Vectors for a [***]. Provided that all decisions of the JSC shall be made by unanimous consent of the JSC, in the event of disagreement, GSK shall have final decision-making authority on the Joint Steering Committee for all activities for the [***] (including whether to continue activities for such [***]). Notwithstanding the foregoing, is understood that in case of compelling safety reasons which could not be resolved by the JSC or the JDC, Telethon-OSR may elect to terminate its involvement with respect to the Development of Licensed Vectors for the [***] clinical activities in accordance with Section 12.3(b) of the Collaboration Agreement shall apply.

3 Amendment of Section 4.2(c) of the Collaboration Agreement (Upon Exercise of Option- Grant of Exclusive License to GSK). Solely with respect to the B-Thal Collaboration Program, Section 4.2(c) of the Collaboration Agreement shall be amended to add the underlined text set forth below. This amended Section 4.2(c) shall not apply to any other Collaboration Program under the Collaboration Program.

"Upon Exercise of Option—Grant of Exclusive License to GSK for the B-Thal Collaboration Program. Subject to the terms and conditions of this Agreement, upon GSK's exercise of the Option for the B-Thal Collaboration Program in accordance with Section 4.2(d) or by operation of Section 12.5 and Telethon-OSR's receipt of the applicable Option Exercise Fee, Telethon-OSR and its Affiliates shall be hereby deemed to have granted and hereby grant to GSK, conditional upon such event, an exclusive, worldwide, sublicenseable (subject to Section 4.14) license (which rights shall be exclusive even as to Telethon-OSR and its Affiliates), in the Territory under ail of Telethon-OSR's and its Affiliates' rights, title and interest in and to the relevant Collaboration Program Exclusively Licensed IP to make, have made, use, sell, offer for sale and import Vectors (for the avoidance of doubt, which shall mean the [***] **("Licensed Vectors"))** and/or Products included under or resulting from the Collaboration Program as and into GSK Products in the Field. For the avoidance of doubt, the license granted upon GSK's exercise of the Option for the B-Thal Collaboration Program shall include the license to make, have made, use, sell, offer for sale and import the Licensed Vectors into GSK products for [***]."

4 Milestone Payments for the [***] in the B-Thal Program. The following [***]-specific milestone payments set out below in Table 1 of this Section 4 of Amendment No. 5 shall apply to the [***] in the B-Thal Program. Following achievement of the corresponding milestone event in the [***] in the Beta-Thal Program, Telethon-OSR shall invoice GSK for the applicable milestone payment and GSK shall make the non-refundable, non-creditable milestone payment to TELETHON-OSR within [***] following receipt of an invoice for such milestone payment. All of the milestones set forth below in this Table 1 of Section 4 shall be payable only once for the [***] in the Beta-Thal Program, regardless of the number of times such milestone event may be achieved.

Milestone Event	**[***] Specific Milestone Events Milestone Payment (€ M)**
[***]	[***]
[***]	[***]

In addition, in the event that the Product developed under this Amendment No. 5 for the treatment of [***] is registered as a separate product from the B-Thal gene therapy Product, and does not reference or incorporate [***], then GSK and Telethon-OSR will meet to reasonably discuss and agree upon the extent to which any of the MAA Approval and Sales Milestones from the B-Thal Program shall also be paid by GSK with respect to the [***] Product.

5 Clarification of Section 6.3(a) of the Collaboration Agreement (Royalties). For the avoidance of doubt, GSK and Telethon-OSR agree that royalties owed by GSK for the B-Thal Program under the Collaboration Agreement shall also include in such royalty calculations royalties on Net Sales of the GSK Product for use in any and all indications (including the [***]).

6 Miscellaneous. In the event of a conflict of terms between this Amendment No. 5 and the Collaboration Agreement, the terms of this Amendment No. 5 shall control. Except as expressly amended by this Amendment No. 5, the Collaboration Agreement (including all of the Side Letter Agreements incorporated therein) shall remain in full force and effect according to its terms. This Amendment No. 5 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 5 will be legal and binding on all Parties. This Amendment No. 5 shall be incorporated not and shall, as of the Amendment No. 5 Effective Date, form part of the Collaboration Agreement between the Parties.

*_*_*_*_*_*_*_*_*_*

[Signatures Follow on Next Page]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 5 to be executed by their duly authorized representatives as of the Amendment No. 5 Effective Date.

For Fondazione Telethon:

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

AMENDMENT NO. 6 TO THE

RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT

This AMENDMENT NO. 6 TO THE RESEARCH AND DEVELOPMENT COLLABORATION AND LICENSE AGREEMENT (the "**Amendment No. 6**") is entered into as of the 7th day of November 2017 (the "**Amendment No. 6 Effective Date**") by and between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor), on the one side and GlaxoSmithKline Intellectual Property Development Limited ("**GSK**") (an Affiliate of Glaxo Group Limited ("**GGL**") and assignee of GGL's rights under the Collaboration Agreement (defined below)). This Amendment No. 6 amends that certain Research and Development Collaboration and License Agreement entered into on October 15, 2010 between GGL, Telethon, Fondazione Centro San Raffaele del Monte Tabor, as amended by Amendment No. 1 on 31 March 2015 (the "**Amendment No. 1**"), and Amendment No. 2 on 4 April 2016 (the "**Amendment No. 2**"), and Amendment No. 3 on 23rd day of September 2016 (the "**Amendment No. 3**"), and Amendment No. 4 on 15 December 2016 (the "**Amendment No. 4**") (the agreement, as amended by Amendments No. 1, No. 2, No. 3, and No. 4 the "**Collaboration Agreement**"), and Amendment No. 5 on July 15th 2017 (the "**Amendment No. 5**"). Capitalized terms used but not defined herein shall have the meaning ascribed to such terms in the Collaboration Agreement. Each of GSK, Telethon, and OSR may be referred to herein as a "Party" and collectively as the "Parties". Telethon and OSR may be referred to herein collectively as "Telethon-OSR".

WHEREAS, the Parties have agreed to amend the Amendment No.2 with respect to certain provisions relating to the B-Thal Collaboration Program; and

WHEREAS, the Parties now desire to enter into this Amendment No. 6 to formalize their agreement with respect to the above referenced subject matter, on the terms and conditions as set forth herein.

NOW, THEREFORE, in consideration of the mutual agreements contained herein and other good and valuable consideration, the sufficiency of which is hereby acknowledged, the Parties agree as follows:

AGREEMENT

1 Payment for Additional Beta Thal Lentiviral Vector Batches. As of this Amendment No 6 Effective Date:

(i) Telethon-OSR and GSK agreed to have a [***] Beta Thal lentiviral vector batch produced at a rate of [***] per batch;

(ii) GSK has already entirely reimbursed the above mentioned amount in accordance with Section 2 of Amendment No. 2;

(iii) on June 27th, 2016 the JSC has elected (upon request from GSK, as agreed by Telethon-OSR) to use [***] of such vector batch for stability studies.

In consideration of the above, the Parties herein agree that, in derogation to Section 2 of the Amendment No. 2, GSK shall not be entitled to deduct [***] of the amount reimbursed with respect to the [***] Beta Thal lentiviral vector batch from future royalties payment due from GSK to Telethon-OSR following to GSK's exercise of the Option with respect to the Beta-Thal Program.

*** Confidential Treatment Requested ***

2 Miscellaneous. This Amendment No. 6 is aimed at amending Amendment No. 2 to the sole extent provided under Section 1 above. In the event of a conflict of terms between this Amendment No. 6 and the Collaboration Agreement, the terms of this Amendment No. 6 shall control. Except as expressly amended by this Amendment No. 6, the Collaboration Agreement (including all of the Side Letter Agreements incorporated therein) shall remain in full force and effect according to its terms. This Amendment No. 6 may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile or pdf transmission of the Amendment No. 6 will be legal and binding on all Parties. This Amendment No. 6 shall be incorporated not and shall, as of the Amendment No. 6 Effective Date, form part of the Collaboration Agreement between the Parties.

*_*_*_*_*_*_*_*_*_*

[*Signatures Follow on Next Page*]

IN WITNESS WHEREOF, and intending to be legally bound hereby, the Parties have caused this Amendment No. 6 to be executed by their duly authorized representatives as of the Amendment No. 6 Effective Date.

For Fondazione Telethon:

By: [***]

Name: [***]

Title: [***]

Ospedale San Raffaele

By: [***]

Name: [***]

Title: [***]

GlaxoSmithKline Intellectual Property Development Limited

By: [***]

Name: [***]

Title: [***]

Milan, 26 June 2012

Glaxo Group Limited
Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex, UK
UB6 oNN
Fax: +44 208 990 4605

To the kind attention of:
Vice President, Associate General Counsel Business Development Transactions and to [***]

Re: MLD Clinical trial

Dear Sirs,

We wish to hereby confirm that HSR-TIGET has recently received additional patients' requests for enrollment in the clinical trials - started under the sponsorship of Fondazione Centro San Raffaele del Monte Tabor ("**San Raffaele**") - related to certain gene therapy of monogenic diseases, which are subject to the Research and Development Collaboration and License agreement signed on October 15, 2010 between Fondazione Telethon ("**Telethon**") and San Raffaele, on one side, and Glaxo Group Limited ("**GSK**"), on the other side (the "**Collaboration Agreement**"). Capitalized terms used, but not defined herein shall have the meaning attributed, to such terms in the Collaboration Agreement.

Namely, as mentioned in previous discussions, Telethon so far received [***] additional requests for enrollment by patients suffering from Metachromatic Leukodystrophy ([***]; such [***] additional patients collectively defined as the "**MLD Additional Patients**").

In consideration of the above, during the Joint Steering Committee on September 28, 2011, we proposed to have GSK reimburse Telethon and San Raffaele for the costs related to the enrolment of the MLD Additional Patients and GSK communicated its willing to proceed accordingly due to its interest in such study, on the terms and conditions set forth herein. We therefore wish here below to sum up in this side letter agreement effective as of this 26 of June, 2012 (the "**Side Letter Agreement**") and which is signed by Telethon in its own name and also in the name and on behalf of San Raffaele based 011 the power of attorney that was granted by San Raffaele to Telethon in writing on 18 January 2012) the proposed terms and conditions as agreed between the parties related thereto.

1. Responsibilities of Telethon.

1.1 **Conduct of Clinical Trials**. The clinical trials for the MLD Additional Patients will be conducted in accordance with the terms and conditions set forth in the Collaboration Agreement, and Telethon and San Raffaele shall remain responsible for the conduct of such clinical trials as set forth in the Collaboration Agreement.

1.2 **Lentiviral Vectors**. Subject to additional terms set forth in Section 2, Telethon shall be responsible for the purchase of additional batches of lentiviral vectors required for the treatment of the MLD Additional Patients and GSK shall pay Telethon for such additional batches of lentiviral vector on the terms set forth in Section 2 below.

2. Costs for the production of additional batches of lentiviral vectors

2.1 GSK undertakes to pay to Telethon the costs, on a pass-through basis, related to the production of additional batches of lentiviral vectors required for the treatment of the MLD Additional Patients ("**Additional Batches**"**),** subject to the terms set forth in the remainder of this Section 2 below.

2.2 It is understood that the production of such

Additional Batches will be done by a third party ("**Third Party**") basing on an agreement executed between Telethon and such Third Party. The Third Party shall be the same Third Party utilized by Telethon for the production of the original batches of lentiviral vector for use in the clinical trials. In the event that Telethon elects to utilize a different Third Party for the production of the Additional Batches, Telethon agrees to inform GSK of such change in advance and to discuss with GSK the applicable diligence to be undertaken by GSK in accordance with confirming the suitability of such different Third Party for the production of such Additional Batches.

2.3 HSR-TIGET will evaluate - at their own and exclusive discretion - the number of Additional Batches required for the treatment of the MLD Additional Patients, provided that HSR-TIGET estimates that up to [***] additional batches of lentiviral vectors will be required. In the event that HSR-TIGET determines that more than [***] Additional Batches are required for the treatment of the MLD Additional Patients, Telethon shall so inform GSK in advance of the initiation of production of such further Additional Batch(es) and GSK and Telethon will discuss and agree upon whether to produce such further Additional Batch(es) and any allocation of costs between the parties for such additional production.

2.4 The costs related to the production of each Additional Batch amount to € [***], plus VAT.

2.5 Telethon will invoice GSK on a pass-through basis for the amounts related to the production of each Additional Batch upon confirmation by the Third Party of the relevant order sent by Telethon. GSK shall pay to Telethon such invoiced amounts within [***] Calendar Days of receipt of such invoice from Telethon. It is understood that in no case will the payment executed by GSK according to this Section 2 be refunded to GSK in the event that GSK does not elect to exercise the Option (as defined under the Collaboration Agreement) with respect to the MLD Collaboration Program.

3. MLD Additional Patients costs

3.1 GSK will pay, in accordance with the terms set forth in this Section 3, [***] of the MLD Additional Patients Costs (the "**GSK MLD Additional Patients Costs**"), up to an amount equal to [[***]Euros (€[***])] (the "**GSK Cost Cap**")**,** subject to GSK's additional payment obligations set forth in Section 4.1 herein. "**MLD Additional Patients Costs**" shall be those costs related to enrollment and treatment of the MLD Additional Patients which include, but are not limited to, MLD Additional Patients cell manipulation costs and hospitalization costs.

3.2 GSK's obligation to pay the GSK MLD Additional Patients Costs, subject to the GSK Cost Cap, will be prior to and independent from the exercise by GSK of the Option (as defined under the Collaboration Agreement) with respect to the MLD Collaboration Program, and in no case will the GSK MLD Additional Patients Costs be refunded to GSK.

3.3 The estimated MLD Additional Patient Costs amounts to € [***] plus VAT, per each MLD Additional Patient, which are understood to be estimations that may be susceptible of possible variations, as follows:

- € [***], plus VAT, per each MLD Additional Patient in the first year;

- € [***], plus VAT, per each MLD Additional Patient in the second year.

3.4 It is understood that the payment of the GSK MLD Additional Patients Costs shall be executed by GSK as follows:

(i) Telethon will invoice GSK for € [***], excluded VAT (i.e. [***] of the estimated MLD Additional Patient Costs) for the first MLD Additional Patient that has already been enrolled and treated within the clinical study) and GSK will pay such invoiced amount to Telethon within [***] days of receipt of such invoice.

(ii) Telethon will invoice GSK for € [***], excluded VAT, (i.e. [***] of the estimated MLD Additional Patient Costs) for each of the remaining [***] MLD Additional Patients following the enrollment of each such MLD Additional Patient and GSK will pay such invoiced amount to Telethon within [***] days of receipt of such invoice.

(iii) Telethon shall be responsible for all MLD Additional Patients Costs, excluding the GSK MLD Additional Patients Costs, subject to the terms of Section 4 below.

3.5 **Unanticipated additional MLD Additional Patient Costs**. In the event that Telethon incurs unanticipated additional MLD Additional Patient Costs in connection

with the conduct of the clinical trials for such MLD Additional Patients, Telethon will inform GSK and GSK and Telethon shall meet and discuss in good faith ways in which such unanticipated additional costs may be reduced or mitigated by the Parties. The allocation of payment responsibility for any unmitigated unanticipated additional MLD Additional Patient Costs will be discussed and agreed between GSK and Telethon.

4. Bonus Milestone Payment to be made by GSK upon exercise of GSK's Option.

4.1 In the event that GSK elects to exercise its Option in accordance with Article 4.2 of the Collaboration Agreement, GSK shall pay solely to Telethon (in addition to payment of the required Option Exercise Fee to be paid as set forth in Section 4.2(d) with respect to the MLD Collaboration Program), in partial consideration for payments related to the inclusion of the MLD Additional Patients as set forth herein, a bonus milestone payment of [***] Euros (€[***]) plus, in accordance with Section 6.2 of this Side Letter Agreement, any VAT amounts owed by Telethon as result of the conduct of such clinical trials, as applicable (the "**MLD Additional Patient Bonus Milestone**") within [***] days of receipt by GSK of an invoice therefor from Telethon.

4.2 In the event that HSR-TIGET has incurred any unanticipated additional MLD Additional Patient Costs as discussed in Section 3.5 of this Side Letter Agreement, the Parties will discuss and agree upon an appropriate allocation of such additional costs between GSK and Telethon and will agree upon an appropriate adjustment to the MLD Additional Patient Bonus Milestone amount accordingly.

5. Other provisions

5.1 The covenants included in this letter shall be intended as a derogation to the provisions of the Collaboration Agreement related to the same subject matter. Except as provided herein, any other provision of the Collaboration Agreement shall remain in full force between the parties thereto. For the avoidance of doubt, the covenants of this Side Letter Agreement shall not entail any amendment to the POC Criteria as defined under Exhibit C of the Collaboration Agreement and to the consequences of their achievement; provided, however that the clinical studies of the MLD Additional Patients to be conducted in accordance with this Side Letter Agreement shall be deemed to be part of the MLD Collaboration Agreement. For the avoidance of doubt, all clinical data arising from treatment of the MLD Additional Patients shall be included in the set of material or relevant clinical and preclinical information to be provided to GSK in the relevant dataroom (as set forth in Article 4.2 of the Collaboration Agreement) prior to the commencement of the Review Period for the MLD Collaboration Program and will be used by GSK as part of their review of the option decision.

5.2 For the avoidance of doubt, GSK's post-Option exercise payment obligations for the MLD Collaboration Program as provided for in the Collaboration Agreement, shall remain unchanged and shall be paid by GSK according to the terms and conditions set forth in the applicable provisions of the Collaboration Agreement.

5.3 Telethon represents and warrants to GSK that Telethon has been granted the appropriate authority and authorization by San Raffaele, pursuant to a currently valid, written agreement between Telethon and San Raffaele dated 19 January 2012, to enter into this Side Letter Agreement in the name of and on behalf of San Raffaele.

5.4 This Side Letter Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

6. Payments

6.1 Unless differently provided under this Side Letter Agreement, GSK shall make all payments due according to said Sections 1-4 within [***] Calendar Days (as defined under Section 1 of the Collaboration Agreement) after receipt by GSK of an invoice from Telethon.

6.2 For VAT, all amounts in this Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of Telethon on account of any royalties or other payments payable to Telethon under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Telethon proof of any such taxes withheld and paid by GSK for the benefit of Telethon, and shall, at Telethon's request, provide reasonable assistance to Telethon in recovering such taxes.

Should you agree with the present document, please sign it for acceptance.

Kind regards,

/s/ Francesca Pasinelli
(Fondazione Telethon)

For acceptance

/s/ Paul Williamson
(Glaxo Group Limited)

From: **GlaxoSmithKline Research and Development Limited** ("**GSK**")
registered in England
980 Great West Road
Brentford, Middlesex
TW8 9GS United Kingdom

To: **Fondazione Telethon** ("**Telethon**"), a non profit entity organized and existing under the laws of Italy, with a registered office located at Via Carlo Spinola 16, 00154 Rome, Italy, and

Fondazione Centro San Raffaele ("**San Raffaele**"), a non profit entity organized and existing under the laws of Italy, with a registered office located at Via Olgettina 60, 20132 Milan, Italy;

Date: [2] **November 2012**

Dear Sirs

Provision of additional services under Research and Development Collaboration and License Agreement

This letter agreement (the "Letter Agreement") is effective as of this ___ day of November, 2012 (the "Letter Agreement Effective Date") by and between GlaxoSmithKline Research and Development Limited ("GSK") (an affiliate of Glaxo Group Limited), and Telethon-San Raffaele. We refer to the Research and Development Collaboration and License Agreement between Glaxo Group Limited on the one hand and Fondazione Telethon, and Fondazione Centro San Raffaele del Monte Tabor on the other hand dated 15 October 2010 (the "Collaboration Agreement"). Words and expressions defined for the purposes of the Collaboration Agreement are to have the same meanings in this letter unless otherwise stated.

We write to record the roles and responsibilities agreed between us relating to the conduct of certain of the research and preclinical Development activities contemplated by the Collaboration Agreement as set out below.

1. Histopathology services

1.1. Section 3.4 of the Collaboration Agreement contemplates that GSK may provide certain preclinical services to assist Telethon-San Raffaele with its Development activities under the Collaboration Agreement, with GSK's preclinical externalization department, SciNovo acting as a conduit between GSK and Telethon-San Raffaele to facilitate the provision of such preclinical services to Telethon-San Raffaele. In connection therewith, Telethon-San Raffaele and GSK have agreed that GSK will provide certain such preclinical services to assist Telethon-San Raffaele in such preclinical activities as set forth in this Letter Agreement, including activities to be performed by GSK's Safety Assessment department in connection therewith.

1.2. It is agreed that GSK, including via SciNovo, shall provide certain pre-clinical services to Telethon-San Raffaele in connection with Telethon-San Raffaele's preclinical Development activities under the Lentivirus-based Collaboration Programs as agree upon, in writing and in advance of initiating such activities ("Services"). The Services shall include, in relation to [***] safety studies and [***] safety studies (collectively, the "Safely Studies"):

(a) the preparation of tissue sections from necropsy samples collected and supplied to GSK by Telethon-San Raffaele;

(b) having GSK pathologists conduct histopathology slide evaluations of those sections; and

(c) having GSK pathologists conduct a peer review of the above mentioned slide evaluations.

(d) providing a full pathology report QA audited of all the delegated phases.

1.3. The Services shall be performed under and on the terms of the Collaboration Agreement, and constitute Development activities carried out on behalf of Telethon-San Raffaele under the Collaboration Agreement.

1.4. Unless otherwise agreed in writing, GSK shall not charge Telethon-San Raffaele for the provision of the Services.

1.5. The parties will agree upon, in writing and in advance of initiating such activities, the extent of the evaluation, number of samples to be evaluated by GSK and the timing of the provision of these Services for each Lentivirus-based Collaboration Program for which such activities are conducted.

2. Ophthalmoscopy services

2.1. Telethon intends to engage the services of a third party sub-contractor, Accelera S.r.l., Viale Pasteur 10, Nerviano (MI) ("Accelera"), 20014, Italy, to undertake ophthalmoscopy services in connection with the Safety Studies in accordance with Section 2.11 of the Collaboration Agreement.

2.2. GSK agrees to reimburse Telethon up to €[***] for each Safety Study, in respect of the fees to be charged by Accelera for undertaking such ophthalmoscopy services.. Reimbursement by GSK shall be executed within [***] of receipt of an invoice from Telethon, corresponding to the relevant invoices issued by Accelera.

2.3. For the avoidance of doubt, Telethon shall remain responsible for the sub-contracted activities of Accelera in accordance with Section 2.11 of the Collaboration Agreement notwithstanding GSK's agreement to reimburse the cost of those services under the terms of this letter.

Except as expressly waived or modified herein, all terms, conditions, covenants, representations, warranties and agreements contained in the Collaboration Agreement remain unchanged and are hereby confirmed and ratified in all respects and shall continue in full force and effect.

Each of the parties acknowledges and agrees that it has not entered into this letter in reliance on any statement or representation of any person (whether a party to this agreement or not) other than as expressly incorporated in this agreement and each of the parties irrevocably and unconditionally waives any right or remedy it may have to claim damages and/or to rescind this letter by reason of any misrepresentation (other than a fraudulent misrepresentation) not contained in this letter.

No amendment, variation, waiver, discharge or termination of this letter shall be effective unless in writing and signed by duly authorised representatives of each of the parties.

This letter shall be governed by and construed in accordance with the laws of England without reference to conflicts of laws principles. All disputes and differences arising out of, or in connection with, this letter shall be determined in accordance with the provisions of Section 13 of the Collaboration Agreement.

If the foregoing represents a true and accurate statement of the Parties' agreement, please confirm your acknowledgement and agreement to the terms set forth above by having a duly authorized representative sign, date and return the duplicate copy of this letter to: [***], Platform Technology and Science, GlaxoSmithKline Research & Development Limited, Park Road, Ware, Hertfordshire SG12 0DP.

Yours faithfully

/s/ Sarah Nesfield

We confirm our agreement to the above.
GlaxoSmithKline Research and Development Limited

for and on behalf of
Fondazione-Telethon

Dated /s/Francesca Pasinelli

for and on behalf of
Fondazione Centro San Raffaele

Dated 05 Nov. 2012 /s/ Guiseppe Banfi

Istituto Scientifico San Raffaele
Via Olgettina 60
Milan
Italy

Fondazione Telethon
Carlo Spinola 16,
00154,
Rome
Italy

TIGET-GLP FACILITIES:SET-UP OF ADDITIONAL DEDICATED ROOMS

Dear Sirs,

Reference is made to that certain Research, Development, Collaboration and License Agreement (the "Collaboration Agreement") entered into on October 15, 2010 by and between Ospedale San Raffaele Sri ("Ospedale") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor; "San Raffaele") with an address at Via Olgettina 60 Milan and Fondazione Telethon, having a registered office at via Carlo Spinola, 16, 00154, Rome, Italy, on the one hand ("Telethon"), and collectively with Ospedale, ("HSR-TIGET"), and Glaxo Group Limited, a company incorporated under the laws of England and Wales with registered number [***], whose registered office is Glaxo Wellcome House, 980 Great West Road, Brentford, London, TW8 9GS, England ("GSK"), on the other hand, pursuant to which the parties agreed to collaborate with respect to certain gene therapy of monogenic diseases. This second side letter agreement (the "Second Side Letter Agreement"), effective as of this 11lh day of June, 2013 (the "Second Side Letter Effective Date") by and between Ospedale and Telethon on the one hand, and GSK on the other hand, sets forth the understanding and agreement of HSR-TIGET and GSK with respect to the expansion of certain animal facilities and use of these latter in connection with the conduct of activities under the Collaboration Agreement, in each case under the terms and conditions as more fully set forth herein. Each of GSK and HSR-TIGET may be referred to herein as a "Party" or collectively as the "Parties", Capitalized terms used, but not defined herein, shall have the meaning attributed lo such terms in the Collaboration Agreement.

AGREEMENT:

1. **Set-up of additional rooms dedicated to GLP studies by HSR-TIGET**. Ospedale San Raffaele has secured to the use of the San Raffaele-Telethon Institute for Gene Therapy certain self-contained area within its animal facility located at Via Olgettina 58, comprising [***] rooms (the "Additional GLP Rooms"), in addition to the rooms previously secured and set up by HSR-TIGET at their sole expense (the "Current GLP Facility" awaiting GLP certification by Italian regulatory authorities). Within the Additional GLP Rooms, [***] will be dedicated to [***] and the [***] will be dedicated to [***]. All together the Current GLP Facility and Additional GLP Rooms will allow HSR-TIGET to conduct multiple GLP studies simultaneously. The agreed-upon plans for the Additional GLP Rooms are set forth in Exhibit A, attached hereto and incorporated

herein by reference (the "Plans"). HSR-TIGET is willing to and will do its best efforts to upgrade (with electric, plumbing and gas work) and equip the Additional GLP Rooms in accordance with the Plans and to provide to the on-going maintenance of the Additional OLP Rooms; however HSR-TIGET will not be held liable by GSK in case of failure by the former to upgrade and equip (the Additional GLP Rooms and to provide on-going maintenance of the Additional GLP Rooms.

2. **Inspection and Accreditation of New Animal Rooms by GSK**. For the purposes of the payments to be made by GSK in accordance with following Article 5:

   - during the set-up (works and equipment) of the Additional GLP Rooms, GSK GLP-QA team shall have the right, but not the obligation, to enter and to inspect the Additional GLP Rooms upon reasonable notice and during normal business hours;
   - upon completion of the Additional GLP Rooms, HSR-TIGET shall inform GSK in writing and GSK shall visit the Additional GLP Rooms for the purpose or conducting an inspection and audit to confirm that such Additional GLP Rooms ore in accordance with the Plans, and with any additional legal, regulatory, or compliance requirements necessary for operation. Such inspection, being aimed at granting the relevant accreditation, will be conducted by GSK GLP-QA team in accordance with GSK's then-current policies and procedures for accreditation of animal research facilities, In the event that GSK identifies any issues with respect to the foregoing, GSK will so inform HSR-TIGET in writing, providing reasonable detail to allow HSR-TIGET to understand the issue. The Parties will thereafter meet and discuss in good faith an appropriate remedy to any such issues, including a possible contribution of GSK of the costs of such remedies.

HSR-TIGET will not conduct GLP activities possibly mandated by GSK within the ADA SCID Program in the Additional GLP Rooms until agreed upon in writing between the Parties. Until then, GLP activities for the ADA SCID Program will be conducted In the Current GLP Facility awaiting certification by Italian regulatory authorities. The Parties hereby agree that the GLP activities within the other Programs of the Collaboration Agreement may be conducted either in the Current GLP Facility or in the Additional GLP Rooms,

3. **Scheduling Development Work**. In the event that a Program under the Collaboration Agreement and another program to be conducted by HSR-TIGET outside the Collaboration Program are being conducted simultaneously and both require the use of the GLP Facilities (Current GLP Facilities and Additional GLP Rooms), HSR-TIGET will make reasonable efforts to prioritize, for a period up to [***] from the accreditation of the Additional GLP Rooms, the Programs being conducted under the Collaboration Agreement in recognition of GSK's contribution to the Additional GLP Rooms as set forth in Paragraph 5 of this Second Side Letter Agreement.

4. **Costs mid Expenses - Generally**. HSR-TIGET have estimated the total costs and expenses related to the upgrading of the Additional GLP Rooms to be [***] Euros (€[***]), exclusive of any VAT (the "Additional GLP rooms Costs").

5. **Payments by GSK**. GSK, having an interest in the expansion of the animal facilities under Article 1 above in view of the possible request to HSR-TIGET for the performance of preclinical studies which may be required to pursue the ADA SCID Program and the

other Programs under the Collaboration Agreement towards the marketing authorization, agrees to pay to HSR-TIGET, in accordance with the terms and conditions set forth herein, a total of [***] Euros (€[***]) in milestone payments in connection with the upgrading of the Additional GLP Rooms (the "Milestone Payments"), such milestone payments to be exclusive of any VAT, which will be handled in accordance with the terms set forth in Section 6.9 of the Collaboration Agreement, as follows:

Milestone Event	Milestone Payment (in Euros (€)
Execution of this Second Side Letter Agreement by all Parties hereto	€ [***]
Completion of the electricity, plumbing and gas works in the Additional GLP Rooms by HSR-TIGET as certified by HSR-TIGET written communication	€ [***]
Accreditation of the Additional GLP Rooms by GSK GLP-QA team	€ [***]

HSR-TIGET will invoice GSK for any milestone payments due under this Paragraph 5 of the Second Side Letter Agreement, and GSK will pay such milestone payments in accordance with the payment terms set forth in Section 6.5 and Sections 6.7 through 6.10 of the Collaboration Agreement. For clarity, the Milestone Payments paid hereunder to HSR-TIGET will be non-refundable, and payment of the Milestone Payments are exclusive and independent from a decision by GSK as to whether to exercise any or all of its Options (as defined under the Collaboration Agreement) for a Program(s) under the Collaboration Agreement.

6. **Care, Welfare, and Ethical Treatment of Animals**. The Parties agree that the following terms regarding the care, use and ethical treatment of animals shall apply to any activities conducted in the New Animal Rooms, and shall also apply generally to the conduct of activities by either Party under the Collaboration Agreement:

6.1 In the performance of the possible activities mandated by GSK, HSR-TIGET agrees to comply with all relevant statutes, legislation, regulations and guidelines for the care, welfare and ethical treatment of animals in the country where the animal studies are being performed. HSR-TIGET further agrees to comply with the "3Rs" Principles - reducing the number of animals used, replacing animals with non-animal methods whenever possible and refining the research techniques used. All work must be conducted in adherence to the core principles for animals identified below. Local customs, norms, practices or laws may be additive to the core principles, but HSR-TIGET agrees to comply and shall procure and ensure that any subcontractors of HSR-TIGET comply, as a minimum, with these core principles: (a) access to species appropriate food and water; (b) access to species specific housing, including species appropriate temperature and humidity levels; (c) access to humane care and a program of veterinary care; (d) animal housing that minimizes the development of abnormal behaviors; (e) adherence to principles of replacement, reduction and refinement in the design of *in vivo* or *ex vivo* studies; (f) review of study design and purpose by institutional ethical review panel; (g) commitment to minimizing pain and distress during *in vivo* and *ex vivo* studies; (h) work is performed by staff trained to conduct the procedures for which they are responsible; (i) training is documented and verified; and

(j) processes are in place to minimize animal use. HSR-TIGET agrees that all animal study protocol shall undergo an ethical review, whether or not required by applicable law, and that written documentation confirming ethical review shall be maintained by HSR-TIGET until [***] after the termination of the each specific preclinical study demonstrating that he review was completed. Those records shall be eligible for inspection by GSK upon reasonable notice and shall be promptly provided to GSK upon request.

6.2 Upon reasonable advance notice, GSK (or its subcontractor/delegate) shall have the right to inspect HSR-TIGET's books and records and HSR-TIGETs facilities (including any facilities used to house animals for research purposes) for the purpose of assessing compliance by HSR-TIGET with the terms of this Article 6 of the Second Side Letter Agreement. The scope of the inspection may include, but need not be limited to, a tour of the facility, the opportunity to view relevant SOPs, training records, building management records, animal health records, ethical review documents, and any other documents reasonably necessary to assess compliance by HSR-TIGET with the terms of this Article 6 of the Second Side Letter Agreement. To the extent that any material deficiencies are identified as the result of such inspection, HSR-TIGET shall endeavor in good faith to take reasonable and practical corrective measures to remedy any such material deficiencies.

6.3 HSR-TIGET shall promptly provide GSK with copies of any regulatory enforcement action or inspection findings issued to HSR-TIGET and relating to systemic failure in the ethical care and treatment of animals, whether such enforcement notion or inspection finding relates to an animal study associated with this Agreement. Ospedale shall have a procedure in place to assess and approve its external suppliers and distributors who supply animals to HSR-TIGET to (i) ascertain and confirm the quality of the animals supplied, (ii) ensure legal requirements for the care and welfare of animals are met and (iii) ensure that only purpose bred animals are used to conduct animal studies, HSR-TIGET shall ensure that those acting for or on its behalf (including but not limited to subcontractors) will comply with the obligations identified in this Article of the Side Letter.

7. **Other provisions**. Except as expressly set forth herein, this Second Side Letter Agreement shall not be construed to modify any of the Parties' respective rights and obligations under the Collaboration Agreement. Neither GSK nor HSR-TIGET may assign this Second Side Letter Agreement, or any rights or obligations of such Party under this Second Side Letter Agreement to a third party without the prior written consent of the other Party. This Second Side Letter Agreement shall be construed and enforced according to the laws of England without reference to conflicts of laws principles. This Second Side Letter Agreement may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile transmission of the signed Second Side Letter Agreement will be legal and binding on both Parties. This Second Side Letter Agreement shall be incorporated into and shall, as of the Second Side Letter Agreement Effective Date, form part of the Collaboration Agreement between the Parties,

If the foregoing represents and accurately reflects your agreement, please have this Second Side Letter Agreement executed by a duly-authorized representative from Ospedale and Telethon and return to GSK for our counter-signature.

Kind regards,

/s/ Nicola Bedin
[Ospedale San Raffaele srl]
[Legal Representative]

/s/ Francesca Pasinelli
Fondazione Telethon
General Manager

WHEREAS, each of the Parties has executed this Second Side Letter Agreement by a duly authorized representative as of the Side Letter Effective Date, as follows:

For **TELETHON-HSR**:

Fondazione Telethon

By: /s/ Francesca Pasinelli

Name: Francesca Pasinelli

Title: General Manager

Istituto Scientifico San Raffaele

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: CEO

For GSK:

Glaxo Group Limited

By: /s/ Paul Williamson

Name: Paul Williamson

Title: Authorised Signatory

Exhibit A

ACTIVITIES FLOW:

[***]

*** Confidential Treatment Requested ***

28 June 2013

OspedaleSan Raffaele Srl
Via Olgettina 60
Milan
Italy

Fondazione Telethon
Carlo Spinola 16,
00154,
Rome
Italy

Re: [***] *Work and Support for* [***] *Activities*

Dear Sirs:

Reference is made to that certain Research, Development, Collaboration and License Agreement (the "Collaboration Agreement") entered into on October 15, 2010 by and between Ospedale San Raffaele Srl ("Ospedale")(successor in interest to Fondazione Centro San Raffaele del Monte Tabor; "San Raffaele") with an address at Via Olgettina 60 Milan and Fondazione Telethon, having a registered office at via Carlo Spinola, 16, 00154, Rome, Italy, on the one hand ("Telethon"), and collectively with Ospedale, ("TIGET"), and Glaxo Group Limited, a company incorporated under the laws of England and Wales with registered number [***], whose registered office is Glaxo Welcome House, 980 Great West Road, Brentford, London, TW8 9GS, England ("GGL"), on the other hand, pursuant to which the parties agreed to collaborate with respect to certain gene therapies for monogenic diseases.

Prior to the Third Side Letter Effective Date (as defined below) TIGET has developed (and owns the relevant intellectual property rights in) certain methods, processes and tests to be used in connection with the activities conducted under this Third Side Letter ("TIGET Methodologies"). TIGET and GlaxoSmithKline Research and Development Limited, an affiliate of GGL ("GSK") now desire to collaborate on certain additional activities to further develop the TIGET Methodologies for the purposes of achieving the Research Goals (as defined under following Section 1) also in support of work being done under the Collaboration Agreement, as set forth more fully herein. This third side letter agreement (the "Third Side Letter Agreement"), effective as of the 28th day of June, 2013 (the "Third Side Letter Effective Date") by and between TIGET on the one hand, and GSK on the other hand, confirms the agreement of TIGET and GSK to conduct and to collaborate on a [***] and on [***]. Each of GSK and TIGET may be referred to herein as a "Party" or collectively as the "Parties". Capitalized terms used, but not defined herein, shall have the meaning attributed to such terms in the Collaboration Agreement.

AGREEMENT:

1. Conduct of Research Activities.

a) Each of GSK and TIGET will use their respective Commercially Reasonable Efforts to conduct the activities (the "Research"), as agreed between the Parties,

for the purpose of achieving the specific research goals set forth in Exhibit A, attached hereto and incorporated herein by reference (the "Research Goals"). TIGET will propose to GSK those specific Research activities to be conducted by TIGET and/or by GSK with respect to the Research and will in good faith consider the reasonable comments and input of GSK with respect to the design and conduct of such activities. TIGET agrees to provide and will provide to GSK within a reasonable time access to the TIGET Methodologies. TIGET therefore hereby grants to GSK a non-exclusive, fully paid-up, royalty-free, sub-licenseable right and license under the TIGET Methodologies (provided however that with respect to such TIGET Methodologies that are not owned exclusively by TIGET, such right and license is granted to the extent TIGET has the legal right to grant such license). Each Party also grants to the other Party a non-exclusive, fully paid-up, royalty-free, worldwide, sublicenseable right and license for any and all purposes under its interest (under the following Section 3) in the methods, processes and tests arising from the conduct of the Research.

b) The Parties may, from time to time, determine that it may be necessary to provide materials from one Party to the other for use in the conduct of the Research. For the avoidance of doubt, the terms of section 2.8 (Material Transfer) of the Collaboration Agreement shall be deemed to apply to any transfer of materials from one Party to the other Party hereunder.

c) All activities conducted by either GSK or TIGET pursuant to this Third Side Letter Agreement shall be deemed to have been conducted within the scope of a Collaboration Program under the Collaboration Agreement.

2. **Reports**. Each Party will provide regular (no less than quarterly, for example via the JDT) summary updates to the other Party on the status of the conduct of the Research, including without limitation a summary of the on-going data and results generated by each Party in the conduct of the Research. Following the completion of the Research, each Party will provide to the other Party a written report of the results of the Research. Each Party will also provide to the other Party, even after GSK possible option exercise on a specific Collaboration Program, a copy of, or access to, all data arising from the conduct of the Research that was conducted under this Third Side Letter, except for instances were data are generated from confidential development programs that are outside of the scope of the Collaboration Agreement.

3. **Ownership of Data and Results**. All of the results and related intellectual property arising from the conduct of the Research by each Party under this Third Side Letter Agreement will be shared between, and jointly owned, according to inventorship contribution by, GSK and TIGET, regardless of which Party conducted the Research activities giving rise to such data and results. Each of GSK and TIGET may use, and may grant non exclusive licenses to a third party to use on their respective behest, such data and results for any and all purposes, provided such use does not conflict with the terms of the Collaboration Agreement. It is hereby understood and agreed that data arising from the Research focused on each individual gene therapy Collaboration Program shall be owned by TIGET and licensed to GSK, upon the exercise by GGL of the option related to the single Collaboration Program as granted to the latter under the Collaboration Agreement.

4. Costs and Expenses. As a contribution for the costs supported by TIGET in conducting the research activities carried out by TIGET prior to the Third Side Letter Effective Date which generated the TIGET Methodologies and as a contribution to the costs for the conduct of the Research hereunder, GSK will pay to TIGET a sum equal to [***] Euros (€[***]) (the "Research Fee") plus VAT if applicable.

5. Method of Payments by GSK. GSK will pay the Research Fee to TIGET in [***] installments to equal a total of [***] Euros ((€[***]) plus VAT if applicable, as follows:

(i) TIGET will invoice GSK on or after the Third Side Letter Effective Date in the amount of [***] Euros (€[***] plus VAT if applicable). Such amount shall constitute the contribution for the costs supported by TIGET in conducting the research activities carried out by TIGET prior to the Third Side Letter Effective Date which generated the TIGET Methodologies;

(ii) after [***] from the Third Side Letter Effective Date - TIGET will invoice GSK for an amount equal to [***] Euros (€[***] plus VAT if applicable) of the Research Fee; and

(iii) upon the [***] the Third Side Letter Effective Date TIGET will invoice the remaining [***] Euros (€[***] plus VAT if applicable),

provided that TIGET shall use the quotas of the Research Fee under (ii) and (iii) solely for the conduct of the Research under this Third Side Letter Agreement and for no other purpose without the express, written consent of GSK.

GSK will pay all such invoices within [***] days from the date of receipt.

For VAT, all amounts in this Third Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] days of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of TIGET on account of any royalties or other payments payable to TIGET under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to TIGET proof of any such taxes withheld and paid by GSK for the benefit of TIGET, and shall, at TIGET's request, provide reasonable assistance to TIGET in recovering such taxes. The terms of sections 6.7 through 6.10 of the Collaboration Agreement shall be deemed to be incorporated by reference herein.

6. Term; Termination. The term of this Third Side Letter Agreement shall commence on the Third Side Letter Effective Date and shall continue for a period of eighteen months thereafter unless earlier terminated by GSK or - TIGET in accordance with the terms set forth in Section 12.2, 12.3 or 12.4 of the Collaboration Agreement (which shall be deemed to apply hereto), or

unless the Collaboration Agreement is terminated in its entirety (in which case the terms of this Third Side Letter Agreement shall be deemed to have been terminated, effective upon the date of termination of the Collaboration Agreement). Termination of this Third Side Letter Agreement shall not relieve a Party of any payment obligations accrued as of the date of notice of termination. In the event of termination of this Third Side Letter Agreement by GSK, for any reason other than a material breach by TIGET, or as a consequence of the termination of the Collaboration Agreement, the license to the TIGET Methodologies granted under Section lb) above shall terminate. In the event that GSK provides notice of termination of this Third Side Letter Agreement at least [***] days prior to the first anniversary of the Third Side Letter Effective Date, GSK shall not have any obligations to pay the third installment of the Research Fee according to Section 6(iii) above Unless this Third Side Letter Agreement is deemed to have been terminated as a result of the termination of the Collaboration Agreement (in which all of the terms set forth herein shall terminate), the terms of paragraphs 1(d), 3, 4 and 8 shall be deemed to survive termination of this Third Side Letter Agreement.

7. Other provisions. Except as expressly set forth herein, this Third Side Letter Agreement shall not be construed to modify any of the Parties' respective rights and obligations under the Collaboration Agreement. Neither GSK nor TIGET may assign this Third Side Letter Agreement, or any rights or obligations of such Party under this Third Side Letter Agreement to a third party without the prior written consent of the other Party. This Third Side Letter Agreement shall be construed and enforced according to the laws of England without reference to conflicts of laws principles This Third Side Letter Agreement may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile transmission of the signed Third Side Letter Agreement will be legal and binding on both Parties. This Third Side Letter Agreement shall be incorporated into and shall, as of the Third Side Letter Effective Date, form part of the Collaboration Agreement between the Parties.

If the foregoing represents and accurately reflects your agreement, please have this Third Side Letter Agreement executed by a duly-authorized representative from Ospedale and Telethon and return to GSK for our counter-signature.

Kind regards,

/s/ Nicola Bedin
[Ospedale San Raffaele srl]
[Legal Representative]

/s/ Francesca Pasinelli
Fondazione Telethon
General Manager

WHEREAS, each of the Parties has executed this Second Side Letter Agreement by a duly authorized representative as of the Side Letter Effective Date, as follows:

Fondazione Telethon

By: /s/ Francesca Pasinelli

Name: Francesca Pasinelli

Title: General Manager

Ospedale San Raffaele Srl

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: Legal Representative

For GSK:

GlaxoSmithKline Research and Development Ltd.

By: /s/ Jonathan Appleby

Name: Jonathan Appleby

Title: Project Leader, Gene Therapy, Rare Diseases, R&D, GSK

Exhibit A

Research Goals

Aims to be pursued

[***]

Execution Copy

Istituto Solentifico San Raffaele
Via Olgettina 60
20132 Milan
Italy

Fondazione Telethon
Via del Magazzini Generall 18/20 00154 Rome
Italy

FOURTH SIDE LETTER AGREEMENT; EXTENSION OF OPTION PERIOD FOR MLD PROGRAM

Dear Sirs,

Reference is made to that certain Research, Development, Collaboration and License Agreement (the "Collaboration Agreement") entered into on October 15, 2010 by and between Ospedale San Raffaele Srl ("Ospedale")(successor in interest to Fondazione Centro San Raffaele del Monte Tabor; "San Raffaele") with an address Vin Olgettina 60 Milan and Fondazione Telethon, having a registered office at via del Magazzini Generali 18/20, 00154, Rome, Italy, on the one hand ("Telethon"), and collectively with Ospedale ("HSR-TIGET"), und Glaxo Group Limited, a company Incorporated under (ho laws of England and Wales with registered number [***], whose registered office is Glaxo Wellcome House, 980 Great West Road, Brentford, London, TW8 9GS, England ("GSK"), on the other hand, pursuant to which the parties agreed to collaborate with respect to certain gene therapy of monogenic diseases.

This fourth side letter agreement (the "Fourth Side Letter Agreement"), effective as of 4th day of September, 2013 (the "Fourth Side Letter. Effective Date") by and between Ospedale and Telethon on the one hand, and GSK on the other hand, sots forth the understanding and agreement of HSR-TIGET and GSK to extend the Review Period for the Metachromatic leukodystrophy Collaboration Program ("MLD") as set forth herein, Each of GSK and HSR-TIGBT may be referred to herein as a "Party" or collectively as the "Parties". Capitalized terms used, but not defined herein, shall have the meaning attributed to such terms in the Collaboration Agreement.

AGREEMENT:

1. Extension of Review Period for GSK'S Option Exorcise for the MLD Collaboration Program, In order to allow GSK to evaluate the MLD Program and to seek appropriate governance committee approvals for the exercise of GSK's Option for the MLD Program, the Parties hereby mutually agree, pursuant to Section 4.2(d)(1) of the Collaboration Agreement, that the Review Period starting on July 18th 2013 during which GSK may elect to exercise Its Option for the MLD Collaboration Program shall be extended until midnight, central European time, on December 1,2013.

2. Other provisions, Except as expressly set forth heroin, this Fourth Side Letter Agreement shall not be construed to modify any of the Parties' respective rights and obligations under the Collaboration Agreement. Neither GSK nor HSR-TIGET may assign this

Fourth Side Letter Agreement, or any rights or obligations of such Party under this Fourth Side Letter Agreement to a third party without the prior written consent of the other Party. This Fourth Side Letter Agreement shall be construed and enforced according to the laws of England without reference to conflicts of laws principles This Fourth Side Letter Agreement may be executed In more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single Instrument. A facsimile transmission of (the signed Fourth Side Letter Agreement will be legal and binding on both Parties. This Fourth Side Letter Agreement shall be Incorporated Into and shall, as of the Fourth Side Letter Agreement Effective Date, form part of the Collaboration Agreement between the Parties.

-*-*-*- Signatures follow on next Page -*-*-*-

If the foregoing represents and accurately reflects your agreement, please have this Fourth Side Letter Agreement executed by a duly-authorized representative from Ospedale and Telethon and return to GSK for our counter-signature.

Kind regards,

/s/ Carlo Russo
Carlo Russo, MD

WHEREAS, each of the Parties has executed this Fourth Side Letter Agreement by a duly authorized representative as of the Fourth Side Letter Effective Dale, as follows:

For TELETHON-HSR:

Fondazlone Telethon

By: /s/ Francesca Pasinelli

Name: Francesca Pasinelli

Tito General Manager

Istituto Scientifico San Raffaele

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: CEO

For GSK:

Glaxo Group Limited

By: /s/ Carlo Russo

Name: Carlo Russo

Title: Interim Head, Rare Disease Development

Execution Copy

Ospedale San Raffaele Srl
Via Olgettina 60
20132 Milan
Italy

Fondazione Telethon
Via dei Magazzini Generall 18/20 00154 Rome
Italy

FIFTH SIDE LETTER AGREEMENT: EXTENSION OF OPTION PERIOD FOR MLD PROGRAM

Dear Sirs,

Reference is made to that certain Research, Development, Collaboration and License Agreement (the "Collaboration Agreement") entered into on October 15, 2010 by and between Ospedale San Raffaele Srl ("Ospedale") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor; "San Raffaele") with an address at Via Olgettina 60 Milan and Fondazione Telethon, having a registered office at via dei Magazzini Generali 18/20, 00154, Rome, Italy, on the one hand ("Telethon"), and collectively with Ospedale ("HSR-TIGET"), and Glaxo Group Limited, a company incorporated under the laws of England and Wales with registered number [***], whose registered office is Glaxo Wellcome House, 980 Great West Road, Brentford, London, TW8 9GS, England ("GSK"), on the other hand, as amended including, In particular, by the Fourth Side Letter dated September 4, 2013, pursuant to which the parties agreed to collaborate with respect to certain gene therapy of monogenic diseases.

This fifth side letter agreement (the "Fifth Side Letter Agreement"), effective as of this 27th day of November, 2013 (the "Fifth Side Letter Effective Date") by and between Ospedale and Telethon on the one hand, and GSK on the other hand, sets forth the understanding and agreement of HSR-TIGET and GSK to extend the Review Period for the Metachromatic leukodystrophy Collaboration Program ("MLD") as set forth herein. Each of GSK and HSR-TIGET may be referred to herein as a "Party" or collectively as the "Parties". Capitalized terms used, but not defined herein, shall have the meaning attributed to such terms in the Collaboration Agreement.

AGREEMENT:

1. **Extension of Review Period for GSK's Option Exercise for the MLD Collaboration Program**. In order to allow GSK to evaluate the MLD Program and to seek appropriate governance committee approvals for the exercise of GSK's Option for the MLD Program, the Parties hereby mutually agree, pursuant to Section 4.2(d)(i) of the Collaboration Agreement, that the Review Period starting on July 18th 2013 during which GSK may elect to exercise its Option for the MLD Collaboration Program shall be extended until midnight, central European time, on December 6, 2013.

2. **Other provisions**. Except as expressly set forth herein, this Fifth Side Letter Agreement shall not be construed to modify any of the Parties' respective rights and obligations under the Collaboration Agreement. Neither GSK nor HSR-TIGET may assign this Fifth Side Letter Agreement, or any rights or obligations of such Party under this Fifth Side Letter Agreement to a third party without the prior written consent of the other Party. This Fifth Side Letter Agreement shall be construed and enforced according to the laws of England without reference to conflicts of laws principles This Fifth Side Letter Agreement may be executed in more than one counterpart, each of which shall be deemed to be an original but all of which taken together shall be deemed a single instrument. A facsimile transmission of the signed Fifth Side Letter Agreement will be legal and binding on both Parties. This Fifth Side Letter Agreement shall be incorporated into and shall, ns of the Fifth Side Letter Agreement Effective Date, form part of the Collaboration Agreement between the Parties.

* * * **Signatures follow on next Page** * * *

If the foregoing represents end accurately reflects your agreement, please have this Fifth Side Letter Agreement executed by a duly-Authorized representative from Ospedale and Telethon mid return to GSK for our counter-signature.

Kind regards,

/s/ Robert Neal
Robert Neal

WHEREAS, each of the Parties has executed this Fifth Side Letter Agreement by a duly authorized representative ns of the Fifth Side Letter Effective Date, as follows:

For TELETHON-HSR:

Fondazione Telethon

By: /s/ Francesca Pasinelli

Name: Francesca Pasinelli

Title: General Manager

Ospedale San Raffaele Srl

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: CEO

For GSK:

Glaxo Group Limited

By: _____

Name: _____

Title: _____

GlaxoSmithKline Research and Development Limited
980 Great West Road
Brentford, London
TW8 9GS
Fax: +44 208 990 4605

To the kind attention of:
Vice President
Associate General Counsel Business Development Transactions
and to:
[***]

Milan, 30 August 2014

Re: MLD Clinical trial

Dear Sirs,

Following Glaxo Group Limited's ("**GSK**") exercise of the option on the Metachromatic Leukodystrophy Research Program on December 6th 2013, according to the Research and Development Collaboration and License agreement signed on October 15, 2010 between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor, San Raffaele), on one side, and Glaxo Group Limited ("**GSK**"), on the other side (the "**Collaboration Agreement**"), we wish to hereby request reimbursement of costs supported by Telethon for vector production of [***] additional LVV ARSA batches and for treatment of [***] patients namely, [***] for which GSK has access to full data.

Capitalized terms used, but not defined herein shall have the meaning attributed to such terms in the Collaboration Agreement and in the letter agreement dated June 26, 2012 related to "MLD clinical trial".

As mentioned in previous discussions, Telethon has so far treated [***] and enrolled [***] MLD patients, namely:

- Telethon and OSR covered all the costs for the first [***] MLD patients ([***]) as per Collaboration Agreement signed on Oct 15th, 2010

- A side letter agreement has been signed on June 26th 2012 according to which GSK accepted to reimburse the clinical costs of [***] additional patients ([***]) for the first [***] years and to reimburse [***] LVV-ARSA batches.
- Telethon has further supported costs for [***] additional LVV ARSA batches production and MLD patients treatments as summarized below:

  a) Patient [***] treated on March 2013 before option exercise: costs of the first year treatment (vector cost has already been reimbursed according to the side letter agreement June 26 2012)

  b) Patients [***] all treated after option exercise and between January and June 2014: cost of treatment

  c) Patient [***] back up performed, after option exercise, on June 2014: cost of back-up

  d) LVV production: [***] additional batches manufactured in 2013 and used to treat patients, [***] as well as a vector stock for treatment of remaining MLD patients. As agreed during a three way meeting between GSK, Telethon-OSR and MolMed in November 2013, to avoid any delay in the MLD and WAS Research Programs progression, clinical study treatments should have been managed as per legacy agreements while waiting for GSK finalizing a contract and quality agreement with MolMed for the LVV production (MLD & WAS) and for the Drug Product preparation, release and RCL tests (patient cells transduction). GSK and Telethon will have then reconciled payments relating to costs for these patients.

  e) For sake of clarity, Patient [***]

We therefore wish here below to sum up in this side letter agreement (effective as of this 30th day of August, 2014 (the "**Sixth Side Letter Agreement**") the proposed terms and conditions as agreed between the parties related thereto.

1. Responsibilities of Telethon.

1.1 Conduct of Clinical Trials. The clinical trials for the MLD Additional Patients has been conducted in accordance with the terms and conditions set forth in the Collaboration agreement up to MLD patient [***]. Future patients will be enrolled under the Clinical Study Agreement signed on May 30th 2014, according to which GSK shall become the financial sponsor of the Study and OSR shall continue to perform the study as the Study sponsor and regulatory sponsor, provided however that, during or after the performance of the Clinical Study, the Parties may agree that regulatory sponsorship of the Study be transferred to GSK.

1.2 **Lentiviral Vectors**. Subject to additional terms set forth in Section 2, Telethon already purchased two additional batches of lentiviral vectors required and used for the treatment of the MLD Patients [***] and usable as a stock vector for treatment of remaining patients and GSK shall reimburse Telethon for such additional batches of lentiviral vector on the terms set forth in Section 2 below.

2. Costs for the production of additional batches of lentiviral vectors

2.1 GSK undertakes to pay to Telethon the costs, related to the production of [***] additional batches of lentiviral vectors required for the treatment of the MLD Additional Patients ("**Additional Batches**"), subject to the terms set forth in the remainder of this Section 2 below.

2.2 The costs related to the production of the two Additional Batches amount to € [***], plus VAT, if applicable.

2.3 Telethon will invoice a total amount of [***] plus VAT if applicable and GSK shall pay to Telethon such invoiced amounts within [***] Calendar Days of receipt of such invoice from Telethon.

3. MLD Clinical Patients costs

3.1 GSK will pay, in accordance with the terms set forth in this Section 3, "**MLD Clinical Patients Costs**" meaning those costs related to enrolment and treatment of the MLD Additional Patients which include, but are not limited to, MLD Clinical Patients cell manipulation costs and hospitalization costs,

3.2 The MLD Additional Patient Costs amounts to:

- € [***], plus VAT if applicable, per treatment and 1 year follow up of patient [***];
- € [***], plus VAT if applicable, per treatment of [***]
- €[***], plus VAT if applicable, per back up of [***]

3.3 It is understood that the payment of the GSK MLD Clinical Patients Costs shall be executed by GSK as follows: Telethon will invoice a total amount of € [***], plus VAT if applicable and GSK will pay such invoiced amount to Telethon within [***] days of receipt of such invoice.

4. Other provisions

4.1 The covenants included in this letter shall be intended as a derogation to the provisions of the Collaboration Agreement related to the same subject matter. Except as provided

herein, any other provision of the Collaboration Agreement shall remain in full force between the parties thereto. For the avoidance of doubt, all clinical data arising from treatment of the MLD Additional Patients shall be included in the set of material or relevant clinical and preclinical information to be provided to GSK.

4.2 For the avoidance of doubt, GSK's post-Option exercise payment obligations for the MLD Collaboration Program as provided for in the Collaboration Agreement, shall remain unchanged and shall be paid by GSK according to the terms and conditions set forth in the applicable provisions of the Collaboration Agreement.

4.3 This Side Letter Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

5. Payments

5.1 Unless differently provided under this Sixth Side Letter Agreement, GSK shall make all payments due according to said Sections 2-4 within [***] Calendar Days (as defined under Section 1 of the Collaboration Agreement) after receipt by GSK of an invoice from Telethon.

5.2 For VAT, all amounts in this Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of Telethon on account of any royalties or other payments payable to Telethon under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Telethon proof of any such taxes withheld and paid by GSK for the benefit of Telethon, and shall, at Telethon's request, provide reasonable assistance to Telethon in recovering such taxes.

Should you agree with the present document, please sign it for acceptance,

Kind regards,

/s/ Francesca Pasinelli
(Fondazione Telethon)

For acknowledgment

(Ospedale San Raffaele)

For acceptance

/s/ Jan Thirkettle

(Date and signature - Glaxo Group Limited)
on behalf of GlaxoSmithKline Research & Development Limited

Sotto l'Alto Patronato
del Presidente
della Repubblica Italiano

Telethon

Glaxo Smith Kline Research and Development Limited
980 Great West Road
Brentford, London
TW8 9GS
Fax: +44 208 990 4605

To the kind attention of:
Vice President
Associate General Counsel Business Development Transactions
and to:
[***]

Milan, 30 August 2014

Re: WAS Clinical trial

Dear Sirs,

Following Glaxo Group Limited's ("**GSK**") exercise of the option on the Wiskott Aldrich Syndrome Research Program on December 6th 2013, according to the Research and Development Collaboration and License agreement signed on October 15, 2010 between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("OSR") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor, San Raffaele), on one side, and Glaxo Group Limited ("**GSK**"), on the other side (the "**Collaboration Agreement**"), we wish to hereby request reimbursement of costs supported by Telethon for vector production of [***] additional LVV WAS batches and for the treatment of [***] patients namely, [***] for which GSK have access to full data.

Capitalized terms used, but not defined herein shall have the meaning attributed to such terms in the Collaboration Agreement.

As mentioned in previous discussions, Telethon has so far treated [***] WAS patients, namely:

- Telethon and OSR covered all the costs for the first [***] WAS patients ([***]) as per Collaboration Agreement signed on Oct 15th, 2010
- Telethon has further supported costs for [***] LVV WAS batches production and [***] WAS patients treatments namely [***] as summarized below:

    a) [***] treated in November 2012 and [***] treated in March 2013 : costs of the first year treatment

    b) [***]: costs of back up and CD34+ purification performed on July 2014

c) LVV production: [***] additional batches manufactured in 2012 and used to treat patients [***] and [***], and [***] additional batches usable as a stock vector for treatment of remaining WAS patients. As agreed during a three way meeting between GSK, Telethon-OSR and MoIMed in November 2013 to avoid any delay in the MLD and WAS Research Programs progression clinical study treatments should have been managed as per legacy agreements while waiting for GSK finalizing a contract and quality agreement with MoIMed for the LVV production (MLD & WAS) and for the Drug Product preparation, release and RCL tests (patient cells transduction). GSK and Telethon will have then reconciled payments relating to costs for these patients.

d) For sake of clarity, Patient [***].

We therefore wish here below to sum up in this side letter agreement (effective as of this 30th day of August, 2014 (the " **Seventh Side Letter Agreement**") the proposed terms and conditions as agreed between the parties related thereto.

1. Responsibilities of Telethon.

1.1. **Conduct of Clinical Trials**. The clinical trial for the WAS Additional Patients has been conducted In accordance with the terms and conditions set forth in the Collaboration Agreement up to patient [***]. Future patients will be enrolled under the Clinical Study Agreement signed on June 30th 2014, according to which GSK shall become the financial sponsor of the Study and OSR shall continue to perform the study as the Study sponsor and regulatory sponsor, provided however that, during or after the performance of the Clinical Study, the Parties may agree that sponsorship of the Study be transferred to GSK.

1.2. **Lentiviral Vectors**. Subject to additional terms set forth in Section 2, Telethon already purchased the additional batches of lentiviral vectors required for the treatment of the [***] , and remaining WAS patients and GSK shall reimburse Telethon for such additional batches of lentiviral vector on the terms set forth in Section 2 below.

2. Costs for the production of additional batches of lentiviral vectors

2.1. GSK undertakes to pay to Telethon the costs, related to the production of additional batches of lentiviral vectors required for the treatment of Patients [***] and remaining WAS Patients ("**WAS Additional Batches**"), subject to the terms set forth in the remainder of this Section 2 below.

2.2. The costs related to the production of the four WAS Additional Batches above amount to € [***], plus VAT if applicable.

2.3. Telethon will invoice a total amount of [***] plus VAT If applicable and GSK shall pay to Telethon such invoiced amounts within [***] Calendar Days of receipt of such invoice from Telethon.

3. WAS Clinical Patients costs

3.1. GSK will reimburse, in accordance with the terms set forth in this Section 3, "**WAS Clinical Patients Costs**" meaning those costs related to enrolment and treatment of the WAS Additional Patients [***] which include, but are not limited to, WAS Clinical Patients cell manipulation costs and hospitalization costs for the first year treatment.

3.2. The WAS Additional Patient Costs amounts to:

- € [***], plus VAT if applicable, per treatment of patient and one year follow up [***];
- € [***] plus VAT if applicable, per back up of patient [***]

3.3. It is understood that the payment of the GSK WAS Clinical Patients Costs shall be executed by GSK as follows: Telethon will invoice a total amount of € [***], plus VAT if applicable and GSK will pay such invoiced amount to Telethon within [***] days of receipt of such invoice.

4. Other provisions

4.1. The covenants included in this letter shall be intended as a derogation to the provisions of the Collaboration Agreement related to the same subject matter. Except as provided herein, any other provision of the Collaboration Agreement shall remain in full force between the parties thereto. For the avoidance of doubt, all clinical data arising from treatment of the WAS Additional Patients shall be included in the set of material or relevant clinical and preclinical information to be provided to GSK.

4.2. For the avoidance of doubt, GSK's post-Option exercise payment obligations for the WAS Collaboration Program as provided for in the Collaboration Agreement, shall remain unchanged and shall be paid by GSK according to the terms and conditions set forth in the applicable provisions of the Collaboration Agreement.

4.3. This Side Letter Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

5. Payments

5.1. Unless differently provided under this Seventh Side Letter Agreement, GSK shall make all payments due according to said Sections 2-4 within [***] Calendar Days (as defined under Section 1 of the Collaboration Agreement) after receipt by GSK of an invoice from Telethon.

5.2. For VAT, all amounts in this Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of Telethon on account of any royalties or other payments payable to Telethon under this Agreement shall

be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Telethon proof of any such taxes withheld and paid by GSK for the benefit of Telethon, and shall, at Telethon's request, provide reasonable assistance to Telethon in recovering such taxes.

***

Should you agree with the present document, please sign it for acceptance.

Kind regards,

/s/ Francesca Pasinelli
(Fondazione Telethon)

For acknowledgement

(Osledale San Raffaele)

For acceptance

/s/ Jan Thirkettle
(Date and signature Glaxo Group Limited)
on behalf of GlaxoSmithKline Research and Development Limited

GlaxoSmithKline Research and Development Limited
980 Great West Road
Brentford, London
TW8 9GS
Fax: +44 208 990 4605

To the kind attention of:
Vice President, Associate General Counsel Business Development Transactions
and to [***], Senior Vice President, R&D Head, GSK Rare Diseases

February 9th, 2015

Re: MLD Clinical trial

Dear Sirs,

Following Glaxo Group Limited's ("**GSK**") exercise of the option on the Metachromatic Leukodystrophy Research Program on December 6th 2013, according to the Research and Development Collaboration and License agreement signed on October 15th, 2010 between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centra San Raffaele del Monte Tabor, San Raffaele), on one side, and Glaxo Group Limited ("**GSK**"), on the other side (the "**Collaboration Agreement**"), Telethon wishes to hereby request reimbursement of costs supported by Telethon on behalf of GSK after Aug 30th, 2014 for the MolMed costs related to the production of [***] additional LVV ARSA vector batch and for treatment (i.e., cell transduction) of [***] patients namely, [***] and collection of back-up material from [***] patients, namely [***] and [***] for which GSK has access to full data.

Capitalized terms used, but not defined herein shall have the meaning attributed to such terms in the Collaboration Agreement and in the letter agreement dated June 26th, 2012 related to "MLD clinical trial".

As mentioned in previous discussions, Telethon has so far treated 16 and enrolled 17 MLD patients, namely:

- Telethon and OSR covered all the costs for the first [***] MLD patients ([***]) as per Collaboration Agreement signed on Oct 15th, 2010

- A side letter agreement has been signed on June 26th 2012 according to which GSK accepted to reimburse the clinical costs of [***] additional patients ([***]) for the first [***] years and to reimburse [***] LVV-ARSA batches.
- A side letter agreement has been signed on August 30th 2014 according to which GSK accepted to reimburse the clinical costs of [***] additional patients:
    a) [***]: costs of the first year treatment (i.e., costs incurred before Option including MolMed costs, clinical and out of pocket costs);
    b) [***]: MolMed costs for treatment (i.e., costs for cell back up and for cell transduction);
    c) [***]: MolMed cost for cell back-up ;
    d) Production of [***] LVV-ARSA batches manufactured on behalf of GSK as GSK stock material; and
    e) For sake of clarity, Patient [***].
- After Aug 30th, 2014, Telethon has further supported MolMed costs on behalf of GSK for [***] additional LVV ARSA vector batch production and treatment of MLD patients (i.e., cell transduction) as summarized below. As agreed during a three way meeting between GSK, Telethon-OSR and MolMed in November 2013, to avoid any delay in the MLD and WAS Research Programs progression, clinical study treatments should have been managed as per legacy agreements while waiting for GSK to finalize a contract and quality agreement with MolMed for the LVV production (MLD & WAS) and for the Drug Product preparation, release and RCL tests (patient cell transduction). GSK and Telethon will have then reconciled payments relating to costs for these patients.
    a) Patient [***] treated on Sept 2014: costs of cell transduction (cell back-up costs have already been reimbursed according to the side letter agreement signed on August 30th 2014).
    b) Patients [***]: costs of treatment (i.e., cell transduction) and back-up ([***] back-ups were performed for patient [***], [***] and [***]; simple back-up without cell selection was performed for patients [***]).
    c) Patient [***]; costs of backup (i.e., [***])
    d) LVV production: [***] additional batch manufactured in November 2014.

Telethon therefore wish here below to sum up in this side letter agreement (effective as of this 9th day of February, 2015 (the "**Eighth Side Letter Agreement**") the proposed terms and conditions as agreed between the parties related thereto.

1. Responsibilities of Telethon.

1.1 Conduct of Clinical Trials. The clinical trial for the MLD Additional Patients has been conducted in accordance with the terms and conditions set forth in the Collaboration Agreement up to MLD patient [***]. Further patients have been enrolled under the Clinical Study Agreement signed between GSK and OSR on May 30th 2014, according to

which GSK shall become the financial sponsor of the Study and OSR shall continue to perform the study as the Study sponsor and regulatory sponsor, provided however that, during or after the performance of the Clinical Study, the Parties may agree that regulatory sponsorship of the Study be transferred to GSK. As a matter of clarity, the clinical costs incurred by OSR after the Option point are covered by the Clinical Study Agreement.

1.2 **Lentiviral Vectors**. Subject to additional terms set forth in Section 2, Telethon already purchased on behalf of GSK [***] additional batch of ARSA lentiviral vector ("**MLD Additional Batch**") usable as a stock vector for treatment of additional patients and GSK shall reimburse Telethon for such additional batch of lentiviral vector on the terms set forth in Section 2 below.

2. Costs for the production of additional batches of lentiviral vectors

2.1 GSK undertakes to pay to Telethon the costs related to the production the MLD Additional Batch required for the treatment of MLD additional patients subject to the terms set forth in the remainder of this Section 2 below.

2.2 The costs related to the production of the MLD Additional Batch amount to €[***], plus VAT, if applicable.

2.3 Telethon will invoice a total amount of €[***] plus VAT if applicable and GSK shall pay to Telethon such invoiced amounts within [***] Calendar Days of receipt of such invoice from Telethon.

3. Molmed costs for MLD patients treatment

3.1 GSK will pay, in accordance with the terms set forth in this Section 3, "**Molmed Costs for MLD Patients Treatment**" meaning those costs related to patient cell manipulation and back-up from bone marrow or leucapheresis of the MLD Additional Patients. For the sake of clarity, Molmed Costs for MLD Patients Treatment do not include clinical costs. Clinical costs are already covered by the Clinical Study Agreement signed between GSK and OSR.

3.2 The MLD Additional Patient Costs amounts to:

- €[***], plus VAT if applicable, for the treatment (cell manipulation) of patient [***] ([***] and [***] used to prepare the IMP);
- €[***], plus VAT if applicable, for the treatment (cell manipulation only of fresh material) and back-up (i.e., [***]) of patient [***];
- €[***], plus VAT if applicable, for the treatment (cell manipulation only of fresh material) and back-up (i.e., [***]) of each patients [***];

- €[***], plus VAT if applicable, for the back-up (i.e., [***]) of patient [***].

3.3 It is understood that the payment of the GSK Molmed Costs for MLD Patients Treatment shall be executed by GSK as follows: Telethon will invoice a total amount of €[***], plus VAT if applicable and GSK will pay such invoiced amount to Telethon within [***] Calendar Days of receipt of such invoice.

4. Other provisions

4.1 The covenants included in this letter shall be intended as a derogation to the provisions of the Collaboration Agreement related to the same subject matter. Except as provided herein, any other provision of the Collaboration Agreement shall remain in full force between the parties thereto. For the avoidance of doubt, all clinical data arising from treatment of the MLD Additional Patients shall be included in the set of material or relevant clinical and preclinical information to be provided to GSK.

4.2 For the avoidance of doubt, GSK's post-Option exercise payment obligations for the MLD Collaboration Program as provided for in the Collaboration Agreement, shall remain unchanged and shall be paid by GSK according to the terms and conditions set forth in the applicable provisions of the Collaboration Agreement.

4.3 This Side Letter Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

5. Payments

5.1 Unless differently provided under this Eighth Side Letter Agreement, GSK shall make all payments due according to said Sections 2-4 within [***] Calendar Days after receipt by GSK of an invoice from Telethon.

5.2 For VAT, all amounts in this Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] days of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of Telethon on account of any royalties or other payments payable to Telethon under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Telethon proof of any such taxes withheld and paid by GSK for the benefit of Telethon, and shall, at Telethon's request, provide reasonable assistance to Telethon in recovering such taxes.

* * *

Should you agree with the present document, please sign it for acceptance. Once fully executed, Eighth Side Letter Agreement shall be effective as of the 9th day of February, 2015.

Kind regards,

/s/ Francesca Pasinelli
(Fondazione Telethon)
General Director

For acknowledgment
For Ospedale San Raffaele:

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: CEO

For acknowledgement and agreement
For GlaxoSmithKline Research and Development Limited:

By: /s/ Martin Andrews

Name: Martin Andrews

Title: SVP GSK Rare Diseases

GlaxoSmithKline Research and Development Limited
980 Great West Road
Brentford, London
TW8 9GS
Fax: +44 208 990 4605

To the kind attention of:
Vice President, Associate General Counsel Business Development Transactions
and to [***], Senior Vice President, R&D Head, GSK Rare Diseases

February 9th, 2015

Re: WAS Clinical trial

Dear Sirs,

Following Glaxo Group Limited's ("**GSK**") exercise of the option on the Wiskott Aldrich Syndrome Research Program on December 6th 2013, according to the Research and Development Collaboration and License agreement signed on October 15th, 2010 between Fondazione Telethon ("**Telethon**") and Ospedale San Raffaele ("**OSR**") (successor in interest to Fondazione Centro San Raffaele del Monte Tabor, San Raffaele), on one side, and Glaxo Group Limited ("**GSK**"), on the other side (the "**Collaboration Agreement**") Telethon wishes to hereby request reimbursement of costs supported by Telethon on behalf of GSK after Aug 30th, 2014 for the MolMed costs related to the vector production of [***] additional LVV WAS batches and for the MolMed costs related to the cell transduction of [***] for which GSK has access to full data.

Capitalized terms used, but not defined herein shall have the meaning attributed to such terms in the Collaboration Agreement.

As mentioned in previous discussions, Telethon and OSR have so far treated [***] WAS patients, namely:

- Telethon and OSR covered all the costs for the first [***] WAS patients ([***]) as per Collaboration Agreement signed on Oct 15th, 2010.
- A side letter agreement has been signed on August 30th 2014 according to which GSK accepted to reimburse the clinical costs of [***] additional patients:
    a) [***] treated in [***] and [***] treated in [***]: costs of the first year treatment (i.e., incurred before Option, including MolMed costs, clinical and out of pocket costs);

b) [***]: only MolMed costs of [***] (i.e., [***]);

c) production of [***] additional LVV WAS vector batches manufactured and used before the Option point and used to treat patients for which GSK has access to full data;

d) production of [***] additional LVV WAS vector batches manufactured on behalf of GSK as GSK stock material;

e) For sake of clarity, Patient [***] is a [***]; and

f) As a matter of clarity, the clinical costs incurred by OSR after the Option point are covered by the Clinical Study Agreement signed between GSK and OSR on June 30th 2014.

- After Aug 30th, 2014, Telethon has further supported MolMed costs on behalf of GSK for [***] additional LVV WAS batches production and treatment (i.e., cell transduction) of an additional WAS patient as summarized below. As agreed during a three way meeting between GSK, Telethon-OSR and MolMed in November 2013, to avoid any delay in the MLD and WAS Research Programs progression, clinical study treatments should have been managed as per legacy agreements while waiting for GSK to finalize a contract and quality agreement with MolMed for the LVV production (MLD & WAS) and for the Drug Product preparation, release and RCL tests (patient cells transduction). GSK and Telethon will have then reconciled payments relating to costs for these patients.

    a) Patient [***] treated on Sept 2014: costs of cell transduction (CD34+ cells purification costs have already been reimbursed according to the side letter agreement signed on August 30th 2014)

    b) LVV production: [***] additional batches manufactured in October 2014 and December 2014.

Telethon therefore wish here below to sum up in this side letter agreement effective as of this 9th day of February 2015 (the "**Ninth Side Letter Agreement**") the proposed terms and conditions as agreed between the parties related thereto.

1. Responsibilities of Telethon.

1.1 Conduct of Clinical Trials. The clinical trial for the WAS Additional Patients has been conducted in accordance with the terms and conditions set forth in the Collaboration Agreement up to patient [***]. Further patients have been enrolled under the Clinical Study Agreement signed on June 30th 2014, according to which GSK shall become the financial sponsor of the Study and OSR shall continue to perform the study as the Study sponsor and regulatory sponsor, provided however that, during or after the performance of the Clinical Study, the Parties may agree that sponsorship of the Study be transferred to GSK. As a matter of clarity, the clinical costs incurred by OSR after the Option point are covered by the Clinical Study Agreement

1.2 **Lentiviral Vectors**. Subject to additional terms set forth in Section 2, Telethon already purchased on behalf of GSK [***] additional batches of WAS lentiviral vector ("**WAS Additional Batches**") usable as a stock vector for the treatment of additional WAS patients and GSK shall reimburse Telethon for such additional batches of lentiviral vector on the terms set forth in Section 2 below.

2. Costs for the production of additional batches of lentiviral vectors

2.1 GSK undertakes to pay to Telethon the costs related to the production of the WAS Additional Batches required for the additional WAS patients, subject to the terms set forth in the remainder of this Section 2 below.

2.2 The costs related to the production of the two WAS Additional Batches amount to €[***], plus VAT, if applicable.

2.3 Telethon will invoice a total amount of €[***] plus VAT if applicable and GSK shall pay to Telethon such invoiced amount within [***] Calendar Days of receipt of such invoice from Telethon.

3. Molmed costs for WAS patient treatment

3.1 GSK will pay, in accordance with the terms set forth in this Section 3, "**Molmed Costs for WAS Patient Treatment**" meaning those costs related to patient cell manipulation of the Additional WAS Patient. For the sake of clarity, Molmed Costs for WAS Patient Treatment do not include clinical costs. Clinical costs are already covered by the Clinical Study Agreement signed between GSK and OSR on June 30th 2014.

3.2 The Molmed costs for WAS patient treatment amount to €[***], plus VAT if applicable, for the treatment (cell manipulation) of patient [***]

3.3 It is understood that the payment of the GSK Molmed Costs for WAS Patient Treatment shall be executed by GSK as follows: Telethon will invoice a total amount of €[***], plus VAT if applicable and GSK will pay such invoiced amount to Telethon within [***] Calendar Days of receipt of such invoice.

4. Other provisions

4.1 The covenants included in this letter shall be intended as a derogation to the provisions of the Collaboration Agreement related to the same subject matter. Except as provided herein, any other provision of the Collaboration Agreement shall remain in full force between the parties thereto. For the avoidance of doubt, all clinical data arising from treatment of the WAS Additional Patients shall be included in the set of material or relevant clinical and preclinical information to be provided to GSK.

4.2 For the avoidance of doubt, GSK's post-Option exercise payment obligations for the WAS Collaboration Program as provided for in the Collaboration Agreement, shall remain unchanged and shall be paid by GSK according to the terms and conditions set forth in the applicable provisions of the Collaboration Agreement.

4.3 This Side Letter Agreement and any dispute arising from the performance or breach hereof including non-contractual obligations shall be governed by and construed and enforced in accordance with the laws of England without reference to conflicts of laws principles.

5. Payments

5.1 Unless differently provided under this Ninth Side Letter Agreement, GSK shall make all payments due according to said Sections 2-4 within [***] Calendar Days after receipt by GSK of an invoice from Telethon.

5.2 For VAT, all amounts in this Side Letter Agreement are stated exclusive of VAT and other indirect taxes. If applicable, the paying Party shall be responsible for the payment of all such appropriately levied taxes to the Party issuing a valid VAT invoice. Should such amounts of VAT be refunded subsequently by the fiscal authorities, the receiving Party shall refund these monies to the paying Party within [***] of receipt. For withholding taxes, any tax paid or required to be withheld by GSK for the benefit of Telethon on account of any royalties or other payments payable to Telethon under this Agreement shall be deducted from the amount of royalties or other payments otherwise due. GSK shall secure and send to Telethon proof of any such taxes withheld and paid by GSK for the benefit of Telethon, and shall, at Telethon's request, provide reasonable assistance to Telethon in recovering such taxes.

* * *

Should you agree with the present document, please sign it for acceptance. Once fully executed, this Ninth Side Letter Agreement shall be effective as of the 9th day of February, 2015.

Kind regards,

/s/ Francesca Pasinelli
(Fondazione Telethon)
General Director

For acknowledgment
For Ospedale San Raffaele:

By: /s/ Nicola Bedin

Name: Nicola Bedin

Title: CEO

For acknowledgement and agreement
For GlaxoSmithKline Research and Development Limited:

By: /s/ Martin Andrews

Name: Martin Andrews

Title: SVP GSK Rare Diseases

Execution Copy

Agreement For Payment of Viral Vector Batch

This Agreement for Payment of Viral Vector Batch (the "**Additional Vector Agreement**") is effective as of this 11th day of December 2015 (the "**Effective Date**") by and between GlaxoSmithKline Research and Development Limited, a company organized under the laws of England and Wales, and located at 980 Great West Road, Brentford, London TW8 9GS ("**GSK**") and Fondazione Telethon, a not for profit foundation organized and existing under the laws of Italy with registered offices located at Via Varese 16b, 00184 Rome, Italy ("**Telethon**"). Each of GSK and Telethon may be referred to herein as a "Party" and collectively as the "Parties."

The Parties entered into a Research and Development Collaboration and License Agreement (the "**Collaboration Agreement**") on October 15, 2010 under which GSK, Telethon, and Ospedale San Raffaele (OSR) Italy and as amended on March 31st 2015 agreed to collaborate on certain cell and gene therapy programs, including a program on Beta Thalassemia. Under the Collaboration Agreement, Telethon together with OSR is responsible for the conduct of certain clinical study activities, including purchasing necessary viral vector used in such activities. Telethon has informed GSK that it has been necessary to order an additional batch of viral vector for use in the Beta Thalassemia study (the "**Additional Vector Batch**") as compared to Telethon's original plan for the study. Telethon ordered this additional batch from MolMed SpA on November 13 2015 and anticipates delivery of the batch on or before October 15 2016. Telethon requested and GSK has agreed to pay a total of [***] € + VAT (the "**Additional Vector Batch Costs**") for this additional batch of viral vector for the Beta Thalassemia program. After the Effective Date of this Additional Vector Agreement, Telethon will invoice GSK for the Additional Vector Batch Costs and GSK will pay such Additional Vector Batch Costs within the first [***] days of the month that is [***] days following the receipt of such invoice.

In the event that further batches of viral vector (in addition to the Additional Vector Batch) may be needed to complete the Beta Thalassemia clinical study (as such clinical study is currently planned and set forth in the clinical study protocol as of the effective date of the Amendment n.1 to the Collaboration Agreement), Telethon will inform GSK and the Parties will discuss and agree upon the timing and number of further batches that may be required. Telethon and GSK will share the costs [***] for any such further batches of viral vector that are agreed by the Parties to be ordered for the Beta Thalassemia clinical study. Telethon's share of such additional batches costs shall be [***] related to the Beta Thalassemia Program.

Acknowledged and agreed by the Parties as of the Effective Date by their duly authorized representatives:

BY: FONDAZIONE TELETHON

By: /s/ Francesca Pasinelli
Name: Dr. Francesca Pasinelli
Title: General Director

Date: 20 Dec 2015

BY: GLAXOSMITHKLINE RESEARCH AND DEVELOPMENT LIMITED

By: /s/ Sven Kili
Name: Dr. Sven Kili
Title: VP, Head of Gene Therapy Development

Date: 20th December 2015

FOR ACKNOWLEDGMENT

OSPEDALE SAN RAFFAELE

By: /s/ Nicola Bedin

Name: Nicola Bedin
Title: Chief Executive Officer

Date: Jan 13 2016

*** Confidential Treatment Requested ***

ORCHARD THERAPEUTICS PLC

2018 EMPLOYEE SHARE PURCHASE PLAN

The purpose of the Orchard Therapeutics plc 2018 Employee Share Purchase Plan (the "**Plan**") is to provide eligible employees of Orchard Therapeutics plc (the "**Company**") and each Designated Subsidiary (as defined in Section 11) with opportunities to purchase Shares. 850,948 Shares in the aggregate have been approved and reserved for this purpose, plus on January 1, 2019 and each January 1 thereafter through January 1, 2028, the number of Shares reserved and available for issuance under the Plan shall be cumulatively increased by the least of (i) 1,500,000 Ordinary Shares, (ii) one percent (1 %) of the number of Shares issued and outstanding on the immediately preceding December 31st, or (iii) such lesser number of Shares as determined by the Administrator. The Plan is intended to constitute an "employee stock purchase plan" within the meaning of Section 423(b) of the U.S. Internal Revenue Code of 1986, as amended (the "**U.S. Code**"), and shall be interpreted in accordance with that intent.

1. Administration. The Plan will be administered by the person or persons (the "**Administrator**") appointed by the Company's Board of Directors (the "**Board**") for such purpose. The Administrator has authority at any time to: (i) adopt, alter and repeal such rules, guidelines and practices for the administration of the Plan and for its own acts and proceedings as it shall deem advisable; (ii) interpret the terms and provisions of the Plan; (iii) make all determinations it deems advisable for the administration of the Plan; (iv) decide all disputes arising in connection with the Plan; and (v) otherwise supervise the administration of the Plan. All interpretations and decisions of the Administrator shall be binding on all persons, including the Company and the Participants. No member of the Board or individual exercising

administrative authority with respect to the Plan shall be liable for any action or determination made in good faith with respect to the Plan or any option granted hereunder.

2. Offerings. The Company will make one or more offerings to eligible employees to purchase Shares under the Plan ("**Offerings**"). Unless otherwise determined by the Administrator, the initial Offering will begin on the Registration Date and will end on the following May 31, 2019 (the "**Initial Offering**"). Thereafter, unless otherwise determined by the Administrator, an Offering will begin on the first business day occurring on or after each June 1 and December 1 and will end on the last business day occurring on or before the following November 30 and May 31, respectively. The Administrator may, in its discretion, designate a different period for any Offering, provided that no Offering shall exceed 27 months in duration or overlap any other Offering.

3. Eligibility. All individuals classified as employees on the payroll records of the Company and each Designated Subsidiary are eligible to participate in any one or more of the Offerings under the Plan, provided that as of the first day of the applicable Offering (the "**Offering Date**") they are customarily employed by the Company or a Designated Subsidiary for more than 20 hours a week and have completed at least 30 days of employment. Notwithstanding any other provision herein, individuals who are not contemporaneously classified as employees of the Company or a Designated Subsidiary for purposes of the Company's or applicable Designated Subsidiary's payroll system are not considered to be eligible employees of the Company or any Designated Subsidiary and shall not be eligible to participate in the Plan. In the event any such individuals are reclassified as employees of the Company or a Designated Subsidiary for any purpose, including, without limitation, common

law or statutory employees, by any action of any third party, including, without limitation, any government agency, or as a result of any private lawsuit, action or administrative proceeding, such individuals shall, notwithstanding such reclassification, remain ineligible for participation. Notwithstanding the foregoing, the exclusive means for individuals who are not contemporaneously classified as employees of the Company or a Designated Subsidiary on the Company's or Designated Subsidiary's payroll system to become eligible to participate in this Plan is through an amendment to this Plan, duly executed by the Company, which specifically renders such individuals eligible to participate herein.

4. Participation.

(a) Participants on Effective Date. Each eligible employee as of the Registration Date shall be deemed to be a Participant at such time. If an eligible employee is deemed to be a Participant pursuant to this Section 4(a), such individual shall be deemed not to have authorized payroll deductions and shall not purchase any Shares hereunder unless he or she thereafter authorizes payroll deductions by submitting an enrollment form (in the manner described in Section 4(c)) within 60 days of the commencement of the Initial Offering. If such a Participant does not authorize payroll deductions by submitting an enrollment form within 60 days of the commencement of the Initial Offering, that Participant will be deemed to have withdrawn from the Plan.

(b) An eligible employee who is not a Participant in any prior Offering may participate in a subsequent Offering by submitting an enrollment form to his or her appropriate payroll location at least 15 business days before the Offering Date (or by such other deadline as shall be established by the Administrator for the Offering).

(c) Enrollment. The enrollment form will (a) state a whole percentage or the amount to be deducted from an eligible employee's Compensation (as defined in Section 11) per pay period, (b) authorize the purchase of Shares in each Offering in accordance with the terms of the Plan and (c) specify the exact name or names in which Shares purchased for such individual are to be issued pursuant to Section 10. An employee who does not enroll in accordance with these procedures will be deemed to have waived the right to participate. Unless a Participant files a new enrollment form or withdraws from the Plan, such Participant's deductions and purchases will continue at the same percentage or amount of Compensation for future Offerings, provided he or she remains eligible.

(d) Notwithstanding the foregoing, participation in the Plan will neither be permitted nor be denied contrary to the requirements of the U.S. Code.

5. Employee Contributions. Each eligible employee may authorize payroll deductions at a minimum of 1 percent up to a maximum of 15 percent of such employee's Compensation for each pay period. The Company will maintain book accounts showing the amount of payroll deductions made by each Participant for each Offering. No interest will accrue or be paid on payroll deductions.

6. Deduction Changes. Except in the event of a Participant increasing his or her payroll deduction from 0 percent during the first Offering as specified in Section 4(a) as may be determined by the Administrator in advance of an Offering, a Participant may not increase or decrease his or her payroll deduction during any Offering, but may increase or decrease his or her payroll deduction with respect to the next Offering (subject to the limitations of Section 5) by filing a new enrollment form at least 15 business days before the next Offering Date (or by such

other deadline as shall be established by the Administrator for the Offering). The Administrator may, in advance of any Offering, establish rules permitting a Participant to increase, decrease or terminate his or her payroll deduction during an Offering.

7. Withdrawal. A Participant may withdraw from participation in the Plan by delivering a written notice of withdrawal to his or her appropriate payroll location. The Participant's withdrawal will be effective as of the next business day. Following a Participant's withdrawal, the Company will promptly refund such individual's entire account balance under the Plan to him or her (after payment for any Shares purchased before the effective date of withdrawal). Partial withdrawals are not permitted. Such an employee may not begin participation again during the remainder of the Offering, but may enroll in a subsequent Offering in accordance with Section 4.

8. Grant of Options. On each Offering Date, the Company will grant to each eligible employee who is then a Participant in the Plan an option ("**Option**") to purchase on the last day of such Offering (the "**Exercise Date**"), at the Option Price hereinafter provided for, the lowest of (a) a number of Shares determined by dividing such Participant's accumulated payroll deductions on such Exercise Date by the lower of (i) 85 percent of the Fair Market Value of the Shares on the Offering Date, or (ii) 85 percent of the Fair Market Value of the Shares on the Exercise Date, (b) a number of Shares determined dividing $50,000 by the Fair Market Value of the Shares on the Offering Date; or (c) such other lesser maximum number of Shares as shall have been established by the Administrator in advance of the Offering; provided, however, that such Option shall be subject to the limitations set forth below. Each Participant's Option shall be exercisable only to the extent of such Participant's accumulated payroll deductions on the Exercise Date.

The purchase price for each share purchased under each Option (the "**Option Price**") will be 85 percent of the Fair Market Value of the Shares on the Offering Date or the Exercise Date, whichever is less.

Notwithstanding the foregoing, no Participant may be granted an option hereunder if such Participant, immediately after the option was granted, would be treated as owning shares possessing 5 percent or more of the total combined voting power or value of all classes of shares of the Company or any Parent or Subsidiary (as defined in Section 11). For purposes of the preceding sentence, the attribution rules of Section 424(d) of the U.S. Code shall apply in determining the share ownership of a Participant, and all shares which the Participant has a contractual right to purchase shall be treated as shares owned by the Participant. In addition, no Participant may be granted an Option which permits his or her rights to purchase Shares under the Plan, and any other employee share purchase plan of the Company and its Parents and Subsidiaries, to accrue at a rate which exceeds $25,000 of the fair market value of such Shares (determined on the option grant date or dates) for each calendar year in which the Option is outstanding at any time. The purpose of the limitation in the preceding sentence is to comply with Section 423(b)(8) of the U.S. Code and shall be applied taking Options into account in the order in which they were granted.

9. Exercise of Option and Purchase of Shares. Each employee who continues to be a Participant in the Plan on the Exercise Date shall be deemed to have exercised his or her Option on such date and shall acquire from the Company such number of whole Shares reserved for the purpose of the Plan as his or her accumulated payroll deductions on such date will purchase at the Option Price, subject to any other limitations contained in the Plan. Any amount remaining in a Participant's account at the end of an Offering solely by reason of the inability to purchase a

fractional share will be carried forward to the next Offering; any other balance remaining in a Participant's account at the end of an Offering will be refunded to the Participant promptly.

10. Issuance of Certificates. Certificates representing Shares purchased under the Plan may be issued only in the name of the employee, in the name of the employee and another person of legal age as joint tenants with rights of survivorship, or in the name of a broker authorized by the employee to be his, her or their, nominee for such purpose.

11. Definitions.

The term "ADSs" means American Depositary Shares, representing Ordinary Shares on deposit with a U.S. banking institution selected by the Company.

The term "Compensation" means the amount of base pay, prior to salary reduction pursuant to Sections 125, 132(f) or 401(k) of the U.S. Code, but excluding overtime, commissions, incentive or bonus awards, allowances and reimbursements for expenses such as relocation allowances or travel expenses, income or gains on the exercise of Company share options, and similar items.

The term "Designated Subsidiary" means any present or future Subsidiary (as defined below) that has been designated by the Board to participate in the Plan. The Board may so designate any Subsidiary, or revoke any such designation, at any time and from time to time, either before or after the Plan is approved by the shareholders. The current list of Designated Subsidiaries is attached hereto as Appendix A.

The term "Fair Market Value of the Shares" on any given date means the fair market value of the Shares determined in good faith by the Administrator; provided, however, that if the ADSs are admitted to quotation on the National Association of Securities Dealers Automated Quotation System ("**NASDAQ**"), NASDAQ Global Market or another national securities

exchange, the determination shall be made by reference to the closing price on such date. If there is no closing price for such date, the determination shall be made by reference to the last date preceding such date for which there is a closing price. Notwithstanding the foregoing, if the date for which the Fair Market Value of the Shares is determined is the Registration Date, the Fair Market Value of the Shares shall be determined based upon the "Price to the Public" (or equivalent) set forth on the cover page for the final prospectus relating to the Company's initial public offering.

The term "Parent" means a "parent corporation" with respect to the Company, as defined in Section 424(e) of the U.S. Code.

The term "Ordinary Shares" mean ordinary shares in the Company, with a nominal value of £0.10 per share.

The term "Participant" means an individual who is eligible as determined in Section 3 and who has complied with the provisions of Section 4.

The term "Registration Date" means the date upon which the registration statement on Form F-1 that is filed by the Company with respect to its initial public offering is declared effective by the Securities and Exchange Commission

The term "Share" means an Ordinary Share and/or the number of ADSs equal to an Ordinary Share, as the context may require

The term "Subsidiary" means a "subsidiary corporation" with respect to the Company, as defined in Section 424(f) of the U.S. Code.

12. Rights on Termination of Employment. If a Participant's employment terminates for any reason before the Exercise Date for any Offering, no payroll deduction will be taken

from any pay due and owing to the Participant and the balance in the Participant's account will be paid to such Participant or, in the case of such Participant's death, to his or her designated beneficiary as if such Participant had withdrawn from the Plan under Section 7. In the case of Participants who are employed in the UK, the termination date of their employment will be the date they give, or are given, notice of termination of their employment unless the Administrator decides that it shall be a later date before the statutory or contractual expiry date of their notice period. An employee will be deemed to have terminated employment, for this purpose, if the corporation that employs him or her, having been a Designated Subsidiary, ceases to be a Subsidiary, or if the employee is transferred to any corporation other than the Company or a Designated Subsidiary. An employee will not be deemed to have terminated employment for this purpose, if the employee is on an approved leave of absence for military service or sickness or for any other purpose approved by the Company, if the employee's right to reemployment is guaranteed either by a statute or by contract or under the policy pursuant to which the leave of absence was granted or if the Administrator otherwise provides in writing.

If a Participant ceases to be employed by the Company or any Subsidiary for any reason whatsoever (including as a result of being wrongfully or unfairly dismissed) they shall not be entitled, and by participating in this Plan they shall be deemed to have waived any possible entitlement, to any sum or benefit accrued or in prospect as a result of that participation and no such loss or curtailment shall form part of any claim for damages for breach of the Participant's contract of employment or compensation for dismissal or any other claim whatsoever.

13. Special Rules. Notwithstanding anything herein to the contrary, the Administrator may adopt special rules applicable to the employees of a particular Designated Subsidiary, whenever the Administrator determines that such rules are necessary or appropriate

for the implementation of the Plan in a jurisdiction where such Designated Subsidiary has employees; provided that such rules are consistent with the requirements of Section 423(b) of the U.S. Code. Any special rules established pursuant to this Section 13 shall, to the extent possible, result in the employees subject to such rules having substantially the same rights as other Participants in the Plan.

14. Optionees Not Shareholders. Neither the granting of an Option to a Participant nor the deductions from his or her pay shall constitute such Participant a holder of the Shares covered by an Option under the Plan until such Shares have been purchased by and issued to him or her.

15. Rights Not Transferable. Rights under the Plan are not transferable by a Participant other than by will or the laws of descent and distribution, and are exercisable during the Participant's lifetime only by the Participant.

16. Application of Funds. All funds received or held by the Company under the Plan may be combined with other corporate funds and may be used for any corporate purpose.

17. Adjustment in Case of Changes Affecting Shares. In the event of a subdivision of outstanding Shares, the payment of a dividend in Shares or any other change affecting the Shares, the number of Shares approved for the Plan and the share limitation set forth in Section 8 shall be equitably or proportionately adjusted to give proper effect to such event.

18. Amendment of the Plan. The Board may at any time and from time to time amend the Plan in any respect, except that without the approval within 12 months of such Board action by the shareholders, no amendment shall be made increasing the number of Shares approved for the Plan or making any other change that would require shareholder approval in

order for the Plan, as amended, to qualify as an "employee stock purchase plan" under Section 423(b) of the U.S. Code.

19. Insufficient Shares. If the total number of Shares that would otherwise be purchased on any Exercise Date plus the number of Shares purchased under previous Offerings under the Plan exceeds the maximum number of Shares issuable under the Plan, the Shares then available shall be apportioned among Participants in proportion to the amount of payroll deductions accumulated on behalf of each Participant that would otherwise be used to purchase Shares on such Exercise Date.

20. Termination of the Plan. The Plan may be terminated at any time by the Board. Upon termination of the Plan, all amounts in the accounts of Participants shall be promptly refunded.

21. Governmental Regulations. The Company's obligation to sell and deliver Shares under the Plan is subject to obtaining all governmental approvals required in connection with the authorization, issuance, or sale of such Shares.

22. Governing Law. This Plan and all Options and actions taken thereunder shall be governed by, and construed in accordance with, the law of England and Wales, applied without regard to conflict of law principles.

23. Issuance of Shares. Shares may be issued upon exercise of an Option from authorized but unissued Shares, from Shares held in the treasury of the Company, or from any other proper source.

24. Tax Withholding. Participation in the Plan is subject to any minimum required tax withholding on income of the Participant in connection with the Plan. Each Participant agrees, by entering the Plan, that the Company and its Subsidiaries shall have the right to deduct

any such taxes from any payment of any kind otherwise due to the Participant, including Shares issuable under the Plan. For this purposes "tax" shall mean Federal, state and local taxes and social security taxes in the US, and their equivalent in any other jurisdiction, for which a Participant is liable by reason of the acquisition, holding or disposal of Shares under the Plan or the receipt of any other benefit in connection with it and which the Company or any Subsidiary is liable to account for on the Participant's behalf.

25. Notification Upon Sale of Shares. Each Participant agrees, by entering the Plan, to give the Company prompt notice of any disposition of Shares purchased under the Plan where such disposition occurs within two years after the date of grant of the Option pursuant to which such Shares were purchased or within one year after the date such Shares were purchased.

26. Effective Date and Approval of Shareholders. The Plan shall take effect upon the date immediately preceding the Registration Date following shareholder approval in accordance with applicable law.

APPENDIX A

Designated Subsidiaries

Orchard Therapeutics (Europe) Limited
Orchard Therapeutics North America
Orchard Therapeutics (Netherlands) B.V.

Exhibit 10.11

DIRECTOR NOMINATION AGREEMENT

THIS DIRECTOR NOMINATION AGREEMENT is dated as of October 18, 2018 (this "**Agreement**"), by and between Orchard Rx Limited (which will re-named and re-registered as a public limited company prior to the IPO (as defined below) at which point the company will be named Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales (the "**Company**"), and Glaxo Group Limited, a company incorporated under the laws of England ("**GSK**"), and is effective as of, and conditioned upon, the closing of the Company's initial public offering ("**IPO**") of American Depository Shares ("**ADSs**"), each ADS representing one ordinary share of the Company, on the Nasdaq Stock Market (the "**Effective Date**").

WHEREAS, GSK, GlaxoSmithKline Intellectual Property Development Ltd. and Oxford Therapeutics (Europe) Limited (previously known as Orchard Therapeutics Limited and now a wholly-owned subsidiary of the Company as a result of a corporate reorganization effected in connection with the IPO) are party to that certain Asset Purchase and License Agreement, dated 11 April 2018 (the "**APA**"), pursuant to which GSK transferred to the Company its portfolio of approved and investigational rare disease gene therapies.

WHEREAS, in light of the foregoing, the parties now desire to set forth the terms of GSK's right to designate a director nominee of the Company following the Company's IPO.

NOW THEREFORE, in consideration of the foregoing premises and the mutual covenants and agreements contained herein, and for other good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties, intending to be legally bound hereby, agree as follows:

1. Nomination of Director.

(a) Effective as of the Effective Date and until the date on which one (1) MLD Royalty Product (as defined in the APA), in respect of which Orchard Therapeutics (Europe) Limited has obtained a marketing authorization or biologics license application and made the first bona fide commercial sale for which revenue has been recognized (the "**Director Nomination Term**"), as further described below, GSK shall have the right to nominate one (1) individual reasonably acceptable to the Company (the "**Nominee**") to serve on the Board of Directors of the Company (the "**Board**") as a Class III director.

Subject to Section 1(b), during the Director Nomination Term, the Board and all applicable committees and subcommittees thereof shall take all action necessary so that the Nominee shall stand for election by the Company's shareholders (the "**Shareholders**") at each annual general meeting of the Company at which Class III directors are required to stand for re-election (each, an "**Annual Meeting**"), it being understood that the next such Annual Meeting is scheduled for the year 2021. The Company agrees to (i) include the Nominee in any proxy statement or written consent prepared by the Company for each such Annual Meeting and recommend and solicit proxies for the election of the Nominee at each such Annual Meeting (and at every adjournment or postponement thereof), (ii) cause all ordinary shares represented by proxies granted to it (or any of its officers, directors or representatives) to be voted in favor of

the Nominee, and (iii) otherwise support the Nominee for election in a manner no less rigorous and favorable than the manner in which the Company supports its other nominees.

(b) As a condition to the nomination of the Nominee in accordance with this Section 1, the Nominee shall provide any information that the Company reasonably requires, including without limitation information required to be disclosed in a proxy statement or other filing under applicable law, stock exchange rules or listing standards and information in connection with assessing eligibility, independence or other criteria applicable to directors under applicable law, stock exchange rules or listing standards. If, at any time (including without limitation, prior to the Nominee's election or re-election to the Board), the Board learns of a Disqualifying Event (as defined below), then the Board may, in its sole discretion, (i) not take any of the actions required by Section 1(a) above (and the Company shall have no obligations pursuant to Section 1(a) above), or (ii) if the Nominee is then serving on the Board, request that the Nominee resign from the Board and any committees thereof (a "**Resignation Request**"). Immediately following delivery of a Resignation Request to the Nominee, the Nominee shall take any and all actions to resign from the Board and any committees thereof which shall be effective immediately and in the absence of such resignation, the Board may remove the Nominee from the Board without the consent of the Nominee. A "**Disqualifying Event**" means any of the following: (x) conduct by the Nominee that is or would reasonably be expected to be materially harmful to the business, interests or reputation of the Company, it being understood that the Nominee's commission of, being indicted or charged with, or making a plea of *nolo contendere* to a felony or a misdemeanor involving moral turpitude, deceit, dishonesty or fraud shall be deemed materially harmful to the business of the Company; or (y) the Nominee's material violation of any provision of any Company Policy (as defined below) or any agreement(s) between the Nominee and the Company (and/or any of its Affiliates (as defined below)). As used herein, "**Affiliate**" means, with respect to any specified person or entity, any other person or entity that directly, or indirectly, controls or is controlled by, or is under common control with, such person or entity.

(c) GSK and the Company acknowledge that the Nominee, subject to and upon election to the Board, shall serve as a member of the Board and shall be governed by the same protections and obligations regarding confidentiality, conflicts of interest, related-party transactions, fiduciary duties, codes of conduct, trading and disclosure policies, director resignation policies, and corporate governance policies of the Company (each, a "**Company Policy**" and collectively, the "**Company Policies**") as other directors (including, for the avoidance of doubt, such obligations as may be imposed by applicable law), and shall be required to preserve the confidentiality of, and not disclose, any non-public information of the Company or any of its subsidiaries, including discussions or matters considered in meetings of the Board or any committees or subcommittees thereof, and shall have the same rights and benefits, including with respect to insurance, indemnification, compensation and fees, as are applicable to all non-employee directors of the Company. Notwithstanding the foregoing, no confidentiality policy or obligation shall preclude the Nominee from sharing information with GSK and its Affiliates, provided that GSK and its Affiliates shall maintain any such information as strictly confidential and shall not disclose any such information to any third party, and provided further that any such information shall be used by GSK and its Affiliates solely for purposes of evaluating, monitoring and managing GSK's investment in the Company and for no other purpose.

(d) As a condition to the Nominee's election or re-election to the Board, as applicable, the Nominee shall agree to sign all documents required to be signed by members of the Board, consistent with past practices, including without limitation the Company's Code of Business Conduct and Ethics and Insider Trading Policy.

(e) Notwithstanding anything to the contrary herein, the Nominee may be excluded from access to any material or meeting or portion thereof if a majority of the directors (excluding the Nominee) of the Board reasonably determine in good faith that such exclusion is reasonably necessary in the event of a conflict of interest.

2. Replacement of Director Designated by GSK. From and after the Effective Date and during the Director Nomination Term, in the event that any Nominee shall fail to be elected at an Annual Meeting, or shall cease to serve as a director for any reason, (i) the vacancy resulting therefrom shall be not be filled until GSK has designated a replacement and, (ii) the directors then in office will elect such designated replacement to fill the resulting vacancy as soon as practicable following GSK's designation of a replacement.

3. Change in Classification of the Board. Except as required by applicable law, stock exchange rules or listing standards, from and after the Effective Date and during the Director Nomination Term, in the event the Company takes any action to alter, remove or amend the classification of the Board into three groups of directors with staggered three-year terms, then the obligations set forth in Section 1 of this Agreement shall apply at any annual meeting or special meeting of the Company at which the director nominated by GSK (including without limitation directors in the same class as such director) shall be entitled to stand for re-election (and Section 1 of this Agreement shall be construed accordingly).

4. Specific Performance. Each of GSK, on the one hand, and the Company, on the other hand, acknowledges and agrees that irreparable injury to the other would occur in the event any of the provisions of this Agreement were not performed in accordance with their specific terms or were otherwise breached and that such injury would not be adequately compensable by the remedies available at law (including the payment of money damages). It is accordingly agreed that GSK, on the one hand, and the Company, on the other hand (in either case, the "**Moving Party**"), shall each be entitled to specific enforcement of, and injunctive relief to prevent any violation of, the terms hereof, and the other will not take action, directly or indirectly, in opposition to the Moving Party seeking such relief on the grounds that any other remedy or relief is available at law or in equity. This Section 4 is not the exclusive remedy for any violation of this Agreement.

5. Severability. If any provision of this Agreement or the application thereof, becomes or is declared by a court of competent jurisdiction to be illegal, void or unenforceable, the remainder of this Agreement will continue in full force and effect and the application of such provision to other persons or circumstances will be interpreted so as reasonably to effect the intent of the parties hereto. The parties further agree to replace such void or unenforceable provision of this Agreement with a valid and enforceable provision that will achieve, to the extent possible, the economic, business and other purposes of such void or unenforceable provision.

6. Term and Termination; Withdrawal from Agreement; Survival. This Agreement will commence as of the Effective Date and shall remain in effect until the end of the Director Nomination Term, unless sooner terminated by mutual agreement or pursuant to the following sentence. GSK may at any time elect, by giving written notice of withdrawal to the Company, to terminate this Agreement. The confidentiality and non-use obligations set forth in Section 1(c) and Sections 4 through 11 shall survive the expiration or termination of this Agreement. All other rights and obligations will terminate upon the expiration or termination of this Agreement.

7. Notices. All notices and other communications hereunder shall be in writing and shall be deemed delivered, given and received (a) when delivered in person, (b) when transmitted by facsimile (with written confirmation of completed transmission), (c) on the third (3rd) business day following the mailing thereof by certified or registered mail (return receipt requested) or (d) when delivered by an express courier (with written confirmation of delivery) to the parties hereto at the following addresses (or to such other address or facsimile number as such party may have specified in a written notice given to the other parties):

(i) if to the Company, to:

Orchard Therapeutics plc
108 Cannon Street
London EC4N 6EU
United Kingdom
Attention: General Counsel

with a copy (which shall not constitute notice) to:

Goodwin Procter LLP
100 Northern Avenue
Boston, MA 02210
Attention: Michael Bison
Facsimile No.: (617) 523-1231

(ii) if to GSK, to:

Glaxo Group Limited
980 Great West Road
Brentford, Middlesex
TW8 9GS, England

with a copy (which shall not constitute notice) to:

King & Spalding International LLP
125 Old Broad Street
London
EC2N 1AR
Attn: Marcus Young

and

SVP BDTT, GSK Legal,
GSK House
980 Great West Road,
Brentford, Middlesex
TW8 9GS, England

Dispute Resolution. The parties irrevocably agree that the courts of England have exclusive jurisdiction to settle any dispute or claim that arises out of or in connection with this Agreement or its subject matter or formation (including non-contractual disputes or claims).

8. Governing Law. The construction, validity and performance of this Agreement and all non-contractual obligations arising from or connected with this Agreement shall be governed by English law.

9. Counterparts. This Agreement may be executed in one or more counterparts, all of which shall be considered one and the same agreement and shall become effective when one or more counterparts have been signed by each of the parties and delivered to the other party, it being understood that all parties need not sign the same counterpart. Until and unless each party has received a counterpart hereof signed by the other party hereto, this Agreement shall have no effect and no party shall have any right or obligation hereunder (whether by virtue of any other oral or written agreement or other communication). Any signature page delivered electronically or by facsimile (including transmission by Portable Document Format or other fixed image form) shall be binding to the same extent as an original signature page.

10. Miscellaneous. This Agreement (a) constitutes the entire agreement among the parties with respect to the subject matter hereof and supersedes all prior agreements and understandings both written and oral, among the parties with respect to the subject matter hereof, and (b) shall not be assigned by operation of law or otherwise, except that GSK may assign its rights and delegate its obligations hereunder to assign its rights and delegate its obligations hereunder to an Affiliate as long as GSK remains ultimately liable for all of GSK's obligations hereunder (or such GSK Affiliate executes a deed of adherence to this Agreement pursuant to which such Affiliate agrees to be bound by the terms hereof).

[The remainder of this page intentionally left blank]

IN WITNESS WHEREOF, this Director Nomination Agreement has been duly executed and delivered by the duly authorized signatories of the parties as of the date hereof.

ORCHARD RX LIMITED

By: _____
Name:
Title:

GSK:

GLAXO GROUP LIMITED

By: _____
Name:
Title:

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the use in this Registration Statement on Form F-1 of Orchard Rx Limited of our report dated August 6, 2018, except for the effects of the revision discussed in Note 14 to the consolidated financial statements, as to which the date is October 23, 2018 relating to the financial statements of Orchard Therapeutics Limited, which appears in this Registration Statement. We also consent to the reference to us under the heading “Experts” in such Registration Statement.

/s/ PricewaterhouseCoopers LLP
Reading, United Kingdom
October 23, 2018