As confidentially submitted to the Securities and Exchange Commission on August 6, 2018.
This draft registration statement has not been publicly filed with the Securities and Exchange Commission and all information herein remains strictly confidential.
Registration Statement No. 333-

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

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 to be registered	**Proposed maximum aggregate offering price(1)**	**Amount of registration fee(2)**
Ordinary shares, nominal value £ per share(3)	$	$

(1) Estimated solely for the purpose of computing the amount of the registration fee pursuant to Rule 457(o) under the Securities Act of 1933, as amended. Includes the aggregate offering price of additional ordinary shares represented by American Depositary Shares, or ADSs, that the underwriters have the option to purchase.

(2) Calculated pursuant to Rule 457(o) under the Securities Act of 1933, as amended, based on an estimate of the proposed maximum aggregate offering price.

(3) These ordinary shares are represented by ADSs, each of which represents ordinary shares 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-).

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 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.

Table of Contents

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 , 2018

Preliminary prospectus

American depositary shares
Representing ordinary shares

Orchard therapeutics

We are offering American Depositary Shares, or ADSs. Each ADS represents ordinary shares. 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 $ and $ 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 12 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 ADSs. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be $, and the total proceeds to us, before expenses, will be $.

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

Wedbush PacGrow

Prospectus dated , 2018

Table of contents

	Page
Market, industry and other data	iii
About this prospectus	iv
Presentation of financial information	v
Prospectus summary	1
Risk factors	12
Special note regarding forward-looking statements	98
Exchange rate information	100
Use of proceeds	101
Dividend policy	103
Corporate reorganization	104
Capitalization	106
Dilution	108
Selected consolidated financial data	110
Management's discussion and analysis of financial condition and results of operations	112
Business	134
Management	188
Related party transactions	200
Principal shareholders	203
Description of share capital and articles of association	205
Description of American depositary shares	225
Shares and ADSs eligible for future sale	237
Material income tax considerations	239
Underwriting	249
Expenses of this offering	258
Legal matters	259
Experts	260
Service of process and enforcement of liabilities	261
Where you can find additional information	263
Index to the financial statements	F-1

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 $1.3529 to £1.00, which was the noon buying rate of the Federal Reserve Bank of New York on December 29, 2017, the last business day of the year ended December 31, 2017. 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.

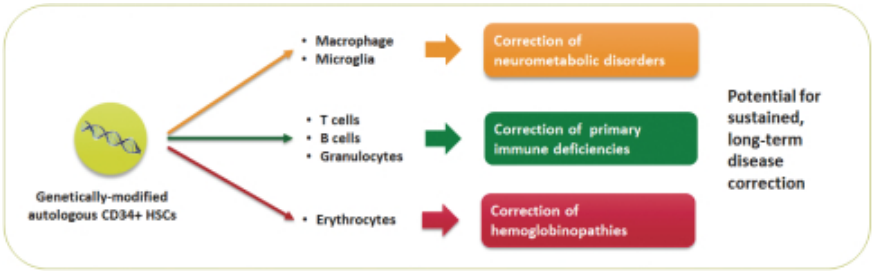
To date, our commercial product and clinical-stage product candidates have been administered in over 140 patients across five different diseases and have accumulated compelling durable efficacy and safety data. These results, in combination with our deep expertise in the development, manufacturing and 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 regulatory submissions for approval of up to three of our most advanced clinical-stage product candidates in the next three years. 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.

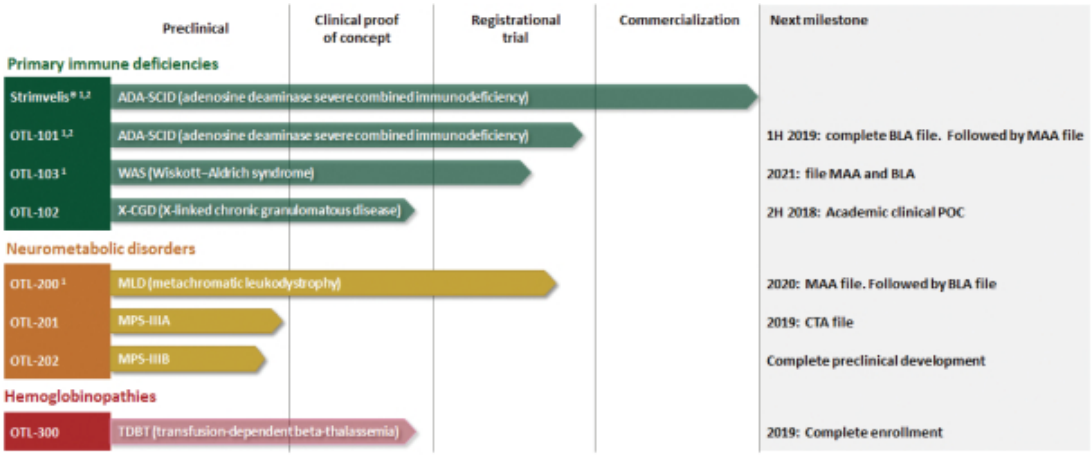
We believe our approach of using lentiviral vectors to genetically modify HSCs has wide-ranging applicability to a large number of indications. The ability of HSCs to differentiate into multiple

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 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. In addition, we believe our long-term clinical follow-up across multiple diseases and with vectors carrying different genes supports the safety of our autologous *ex vivo* gene therapy approach. This stands in contrast to the current standard of care for many of the diseases that we are initially targeting, where the use of allogeneic HSC transplantation, or HSCT, carries a significant risk of complications and mortality, and other treatment options such as chronic enzyme replacement therapy, or ERT, have limited efficacy.

We have a broad and advanced portfolio of wholly-owned commercial and development stage products and product candidates. We currently anticipate filing one product for regulatory approval in each of the next three years.



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

Three of our clinical-stage product candidates are currently in registrational trials and have shown compelling efficacy and safety data:

- OTL-101 is our product candidate for ADA-SCID, a rare, life-threatening inherited disease of the immune system. Drug product has been administered in 61 patients with a follow-up of up to six years post-treatment. The combined data from our two principal trials indicate overall survival of 100% with event-free survival of 97%. We expect to initiate a rolling BLA for OTL-101 with the FDA during the second half of 2018 and to complete submission in the first half of 2019, followed by an MAA submission with the EMA. 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.
- OTL-200 is our product candidate for MLD, a rare and rapidly progressive neurometabolic disorder. OTL-200 has evidenced sustained expression of the deficient ARSA enzyme, with significant long-term motor and cognitive improvements in most patients. These results exhibit the ability of our approach to target complex diseases which involve the central nervous system. There are no approved therapies for treatment of MLD available today. We plan to submit an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA.
- 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 achieved an overall survival of 100% in eight patients with a follow-up of up to eight-years post-treatment, with clinically meaningful reductions in bleeding events and infections observed at three years. We plan to submit an MAA with the EMA and a BLA with the FDA for OTL-103 in 2021.

Beyond these three lead product candidates, our other clinical-stage programs, OTL-102 for X-CGD and OTL-300 for transfusion-dependent beta-thalassemia, or TDBT, continue to generate favorable safety and efficacy data in initial clinical trials. 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 filing 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 number of patients treated and maximum survival follow-up as of July 2018 across the lead programs in our franchise areas.

Franchise	Program	Patients Treated[1]	Maximum survival follow-up
Primary immune deficiencies	**OTL-101** (ADA-SCID)	61	~6 years
	Strimvelis® (ADA-SCID)	24	~18 years
	OTL-103 (WAS)	15	~8 years
	OTL-102 (X-CGD)	10	~3 years
Neurometabolic disorders	**OTL-200** (MLD)	30	~8 years
Hemoglobinopathies	**OTL-300** (TDBT)	9	~3 years
Total		149 patients	

(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.

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 will ultimately be exchanged 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. 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. 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 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 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 or other 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 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. 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	ADSs, each representing ordinary shares
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 ADSs from us.
Ordinary shares to be outstanding immediately after this offering	ordinary shares (or ordinary shares if the underwriters exercise in full their option to purchase an additional ADSs).
American depositary shares	Each ADS represents ordinary shares, nominal value £0.00001 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	
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 $ based on an assumed initial public offering price of $ 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.
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 number of our ordinary shares to be outstanding after this offering gives effect to the corporate reorganization described under the "Corporate reorganization," prior to the closing of this offering, is based on of our ordinary shares outstanding as of June 30, 2018, and gives effect to the conversion of all of our outstanding preferred shares into ordinary shares immediately prior to the closing of this offering, and excludes:

- ordinary shares issuable upon the exercise of options for ordinary shares outstanding as of June 30, 2018, with a weighted-average exercise price of $ per share;
- an additional ordinary shares reserved for issuance under our 2016 Employee Share Option Plan, or the 2016 Plan, as of June 30, 2018, which shares will no longer be reserved following this offering;
- an additional 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 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 preferred shares into an aggregate of ordinary shares upon the closing of this offering;
- no issuance or exercise of outstanding options after June 30, 2018;
- a 1-for- reverse split of our ordinary shares effected on , 2018; and
- no exercise by the underwriters of their option to purchase up to 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 and the selected consolidated balance sheet data as of December 31, 2017 from our audited consolidated financial statements included elsewhere in this prospectus. We prepare our consolidated financial statements in accordance with U.S. GAAP.

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 December 29, 2017, the last business day of the year ended December 31, 2017, the representative exchange rate was £1.00 = $1.3529.

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,	
	2016	2017
	(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
General and administrative	2,997	5,985
Total operating expenses	19,203	38,512
Loss from operations	(19,203)	(38,512)
Other income (expense), net	138	(1,179)
Net loss before income taxes	(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

	As of December 31, 2017		
	Actual	Pro Forma(1)	Pro Forma As adjusted(2)
		(in thousands)	
Consolidated Balance Sheet Data:			
Cash	$89,856	$ 242,200	$
Working capital(3)	83,466	235,810	
Total assets	97,294	249,638	
Total shareholders' (deficit) equity	86,405	238,749	

(1) The pro forma balance sheet data gives effect to (i) the sale of 616,641 shares of Series B preferred shares in January 2018 for gross cash proceeds of $3.3 million of which $1.0 million was received in December 2017 and (ii) the sale of 17,421,600 shares of Series C preferred shares in August 2018 for gross cash proceeds of approximately $150.0 million.

(2) Each $1.00 increase (decrease) in the assumed initial public offering price of $ 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, total shareholders' equity and total capitalization by $ 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 $ million, assuming no change in the initial public offering price per ADS.

(3) 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 and $39.7 million for the years ended December 31, 2016 and 2017, respectively. We historically have financed our operations primarily through private placements of our 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 our agreement with GSK, 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 initiate a rolling BLA for OTL-101 for ADA-SCID with the FDA during the second half of 2018 and to complete submission during the first half of 2019, followed by an 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 filings, 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 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. 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 benefit has been observed in clinical trials to date for OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, there can be no assurance that the results seen in previous or ongoing 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 serious adverse events 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 anticipate initiating a rolling BLA for OTL-101 for ADA-SCID with the FDA during the second half of 2018, but 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. We anticipate initiating a rolling BLA for OTL-101 for ADA-SCID with the FDA during the second half of 2018. We plan to complete the BLA filing in the first half of 2019. 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.

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 does not find the results from these trials to be sufficiently persuasive to support a BLA submission. The FDA may also require that we conduct a longer follow-up period of patients treated with our product candidates prior to accepting our BLA submission. These same factors may come into play with respect to other regulators such as the EMA.

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 serious adverse events 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 filing 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. 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. We are currently evaluating our product candidates and plan to seek marketing approval using drug product that is manufactured 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.

As part of any BLA or MAA submission, we will need to demonstrate comparability 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 and comparability between drug product that has been cryopreserved and fresh drug product. We plan to submit *in vitro* comparability analyses as part of these regulatory submissions, and we are conducting clinical trials in order to generate clinical data to support these *in vitro* comparability analyses. We cannot assure you that the FDA, EMA or other regulatory authority will not require us to conduct additional *in vitro* 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 *in vitro* comparability analyses or clinical trials will be sufficiently robust to support approval or our product candidates using these production methods and processes. For example, the EMA has advised us that it will require clinical data using drug product that has been cryopreserved as part of our planned MAA 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 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 filing 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 (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 our asset purchase and license agreement, or the GSK Agreement, with Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD, or, together, GSK, 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, OTL-102 for X-CGD and OTL-201 for MPS-IIIA from the FDA and EMA and for 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, OTL-102 for X-CGD and OTL-201 for MPS-IIIA from the FDA and EMA and for 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 a marketing authorization application to 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 products 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 products 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 a lentiviral-based autologous *ex vivo* gene therapy for TDBT. bluebird bio has publicly announced that it expects to file an MAA in a patient population with non ß0/ß0 TDBT for this product candidate during the second half of 2018, with a future BLA planned in the United States. 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 adenovirus AAV-10 vector in a Phase I/II 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 Phase I/II clinical trials with autologous *ex vivo* lentiviral gene therapy.
- **X-CGD:** We are aware that Généthon is sponsoring a Phase I/II 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 Phase I 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, *in vitro* 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 filings, 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 CGMPs. 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 or other 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 ACA or PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, or 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 serious adverse events 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, the U.S. Foreign Corrupt Practices Act 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 U.K. Bribery Act 2010, or the Bribery Act, the U.S. Foreign Corrupt Practices Act of 1977, as amended, or 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, Centers for Medicare and Medicaid Services, 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 European Economic Area 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

Third parties may claim that we are infringing, misappropriating or otherwise violating their intellectual property rights, 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 our 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 holder 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.

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 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 % of our ordinary shares and, upon closing of this offering, that same group will beneficially own approximately % 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, we will have outstanding ordinary shares (including ordinary shares represented by the ADSs), approximately of which 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 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.

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.

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."

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 $ per ADS, based on the initial public offering price of $ 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 , 2018. Further, investors purchasing ADSs in this offering will contribute approximately % of the total amount invested by shareholders since our inception, but will own only approximately % 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, we will have outstanding ordinary shares based on the number of ordinary shares outstanding as of August 2, 2018, (or ordinary shares if the underwriters exercise their option to purchase additional ADSs in full). This includes the ADSs that we are selling in this

offering (or 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 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 million 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, ordinary shares reserved for issuance upon the exercise of existing options outstanding as of August 2, 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 Securities and Exchange Commission, or 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 U.S. Securities Exchange Act of 1934, as amended, or 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 of 2002 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 generally accepted accounting principles in the United States, or U.S. GAAP, during these periods. Specifically, the findings relates to our internal control infrastructure as of December 31, 2016 and 2017 where we did not design or implement sufficient processes, controls and other review procedures to evaluate the recognition and accrual of research and development related expenses and reimbursements for periods ended December 31, 2016 and 2017. As a result, there were adjustments required in connection with closing our books and records and preparing our 2016 and 2017 financial statements.

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 H.R. 1, known as 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 have not made a determination regarding if we are, or have been, a CFC for the current or prior taxable years, and we may be a CFC for the current taxable year or a following 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 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 passive foreign investment company, or 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 have not made a determination regarding if we will be, or have been, a PFIC for the current taxable year or in prior taxable years. 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 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. incorporation 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.

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, and will continue to be, 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.

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 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 July 27, 2018)	1.3118	1.3685	1.2987	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	1.3755	1.4236
June 2018	1.3258	1.3611
July 2018 (through July 27, 2018)	1.2987	1.4332

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 July 27, 2018, the noon buying rate of the Federal Reserve Bank of New York for the U.S. dollar was £1.00 to $1.3118.

Use of proceeds

We estimate that the net proceeds to us in this offering will be $ 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 $ 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 $ 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 $ per ADS would increase (decrease) the net proceeds to us from this offering by $ 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 $ 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 $ million to fund the ongoing development of our product candidates, including completing registrational trials and filing 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 $ 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 $ 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 for at least the next months. 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 ordinary shares of £0.00001 each; Series A preferred shares of £0.00001 each; Series B preferred shares of £0.00001 each; Series B-2 preferred shares of £0.00001 each; and Series C preferred shares of £0.00001 each. Prior to the effectiveness of the registration statement of which this prospectus forms a part, the shareholders of Orchard Therapeutics Limited will exchange 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 will become the sole shareholder of Orchard Therapeutics Limited.

Bonus issue and consolidation of shares in Orchard Rx Limited

Immediately after this share exchange, Orchard Rx Limited shall capitalize the sum of £ standing to the credit of Orchard Rx Limited’s share premium account and apply such sum in paying up in full ordinary shares of £0.00001 each; Series A preferred shares of £0.00001 each; Series B preferred shares of £0.00001 each; Series B-2 preferred shares of £0.00001 each; and Series C preferred shares of £0.00001 each by means of a bonus issue on the basis of) new shares for each existing share. Immediately following the completion of the bonus issue, Orchard Rx Limited shall consolidate its ordinary shares of £0.00001 each into ordinary shares of £ each; Series A preferred shares of £0.00001 each into Series A preferred shares of £ each; Series B preferred shares of £0.00001 each into Series B preferred shares of £ each; Series B-2 preferred

shares of £0.00001 each into Series B-2 preferred shares of £ each; and Series C preferred shares of £0.00001 into Series C preferred shares of £ each.

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

Following Orchard Therapeutics Limited becoming a wholly owned subsidiary of Orchard Rx Limited, prior to the completion of this offering, Orchard Rx Limited will re-register as a public limited company. Such re-registration will require the passing of special resolutions by the 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 shall change its name to Orchard Therapeutics (Europe) Limited.

Certain further resolutions will be required to 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.”

Prior to the completion of this offering, all preferred and ordinary shares will convert into an aggregate of shares of a single class of ordinary shares of Orchard Therapeutics plc. The ratio for the exchange of each class of preferred shares of Orchard Therapeutics plc into ordinary shares of Orchard Therapeutics plc will be determined based on the final price per ADS in this offering. Assuming an initial public offering price of $ per ADS, which is the midpoint of the price range set forth on the cover page of this prospectus, each class of the preferred shares of Orchard Therapeutics plc will be exchanged for ordinary shares of Orchard Therapeutics plc according to the following ratios:

- each Series A preferred share will be converted into ordinary shares;
- each Series B preferred share will be converted into ordinary shares;
- each Series B-2 preferred share will be converted into ordinary shares;
- each Series C preferred share will be converted into ordinary shares;

Therefore, upon consummation of the corporate reorganization and prior to the completion of this offering, assuming an initial public offering price of $ per ADS, the current shareholders of Orchard Therapeutics Limited will hold an aggregate of ordinary shares of Orchard Therapeutics plc. In the event of a $1.00 increase in the assumed initial public offering price per ADS to $ per ADS, the current shareholders of Orchard Therapeutics Limited will hold an aggregate of ordinary shares of Orchard Therapeutics plc. In the event of a $1.00 decrease in the assumed initial public offering price per ADS to $ per ADS, the current shareholders of Orchard Therapeutics Limited will hold an aggregate of ordinary shares of Orchard Therapeutics plc.

Capitalization

The following table sets forth our cash and capitalization of Orchard Therapeutics Limited as of December 31, 2017 on:

- an actual basis; and
- a pro forma basis to give effect to:
  - our sale of 616,641 shares of Series B preferred shares in January 2018 and conversion into an aggregate of 616,641 ordinary shares upon closing if this offering;
  - our issuance of 437,049 ordinary shares in January 2018 to Généthon pursuant to our license agreement;
  - our issuance of 15,563,230 Series B-2 preferred shares in April 2018 to GSK pursuant to the GSK Agreement and conversion into an aggregate of 15,563,230 ordinary shares upon closing of this offering;
  - our issuance of 188,462 ordinary shares in June 2018 to Oxford Biomedica pursuant to our license agreement;
  - our sale of 17,421,600 shares of Series C preferred shares in August 2018 and conversion into an aggregate of 17,421,600 ordinary shares upon closing of this offering;
  - the conversion of all outstanding preferred shares as of December 31, 2017 into an aggregate of 41,581,513 ordinary shares upon the closing of this offering;
  - the filing and effectiveness of our amended and restated certificate of incorporation upon the closing of this offering; 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 ADSs in this offering.

The pro forma as adjusted calculations assume an initial public offering price of $ 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 December 31, 2017 (in thousands, except share and per share data)		
	Actual	Pro forma	Pro forma as adjusted(1)
Cash	$ 89,856	$ 242,200	$
Shareholders’ equity:			
Convertible preferred shares, £0.00001 par value; 42,198,154 shares authorized, 41,581,513 shares issued and outstanding as of December 31, 2017; no shares authorized, issued and outstanding, pro forma; no shares authorized, issued and outstanding, pro forma as adjusted	134,069	—	
Ordinary shares, £0.00001 par value; authority to allot up to a maximum nominal value of £675,413, 11,154,720 shares issued and outstanding, actual; 86,976,340 shares issued and outstanding, pro forma; shares issued and outstanding, pro forma as adjusted	—	—	
Additional paid-in capital	7,610	387,414	
Accumulated other comprehensive (loss) income	4,127	4,127	
Accumulated deficit	(59,401)	(152,792)	
Total shareholders’ equity	86,405	238,749	
Total capitalization	$ 86,405	$ 238,749	

(1) Each $1.00 increase (decrease) in the assumed initial public offering price of $ 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, total shareholders’ equity and total capitalization by $ 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 $ million, assuming no change in the assumed initial public offering price per ADS.

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

- 5,223,443 ordinary shares issuable upon the exercise of share options outstanding as of December 31, 2017, with a weighted average exercise price of $0.96 per share;
- 2,942,141 ordinary shares reserved for issuance under our 2016 Employee Share Option Plan, the 2016 Plan, as of December 31, 2017, which shares will no longer be reserved following this offering;
- 169,615 ordinary shares issuable to Oxford BioMedica U.K. upon the achievement of certain performance milestones; or
- any ordinary shares reserved for future issuance under our 2018 Equity 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.

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 December 31, 2017, we had a historical net tangible book value of $ million, or $ per ordinary share (equivalent to $ 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 December 31, 2017.

After giving effect to (i) our corporate reorganization and (ii) the sale of ADSs in this offering at an assumed initial public offering price of $ 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 December 31, 2017 would have been $ per ordinary share, or $ per ADS. This represents an immediate increase in pro forma as adjusted net tangible book value of $ per ADS to new investors and immediate dilution of $ 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		$
Historical net tangible book value per ADS as of December 31, 2017	$	
Effect attributable to our corporate reorganization and new investors purchasing ADSs in this offering		
Pro forma as adjusted net tangible book value per ADS as of December 31, 2017		
Dilution per share to new investors purchasing ADSs in this offering		$

Each $1.00 increase (decrease) in the assumed initial public offering price of $ 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 December 31, 2017 after this offering by $ per ADS, and would increase (decrease) dilution to new investors by $ 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 December 31, 2017 after this offering by $ per ADS, and would increase (decrease) dilution to new investors by $ 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 $, the increase in net tangible book value per ADS to existing shareholders would be $ and the immediate dilution in net tangible book value per ADS to new investors in this offering would be $.

The following table summarizes, on the pro forma as adjusted basis described above as of December 31, 2017, 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 $ 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		%	$	%	$
New investors participating in this offering					$
Total		100.0%	$	100.0%	

Each $1.00 increase (decrease) in the assumed initial public offering price of $ 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 $ million and, in the case of an increase, would increase the percentage of total consideration paid by new investors by percentage points and, in the case of a decrease, would decrease the percentage of total consideration paid by new investors by 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 $ million and, in the case of an increase, would increase the percentage of total consideration paid by new investors by percentage points and, in the case of a decrease, would decrease the percentage of total consideration paid by new investors by 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 % of the total number of ordinary shares outstanding after the offering, and the number of shares held by new investors will be increased to , or % 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 selected consolidated balance sheet data as of December 31, 2016 and 2017 from our audited consolidated financial statements included elsewhere in this prospectus. We prepare our consolidated financial statements in accordance with U.S. GAAP.

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 December 29, 2017, the last business day of the year ended December 31, 2017, the representative exchange rate was £1.00 = $1.3529.

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,	
	2016	2017
	(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
General and administrative	2,997	5,985
Total operating expenses	19,203	38,512
Loss from operations	(19,203)	(38,512)
Other income (expense), net	138	(1,179)
Net loss before income taxes	(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

	As of December 31,	
	2016	2017
	(in thousands)	
Consolidated Balance Sheet Data:		
Cash	$ 3,497	$ 89,856
Working capital(1)	163	83,466
Total assets	4,283	97,294
Convertible preferred shares in temporary equity	16,970	—
Total shareholders' (deficit) equity	(16,524)	86,405

(1) 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. 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 140 patients across five different diseases and have accumulated compelling durable efficacy and safety data. 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 initiate a rolling BLA with the FDA for our product candidate OTL-101, a lentiviral gene therapy for ADA-SCID, during the second half of 2018, and to complete submission in the first half of 2019 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 continue to generate favorable safety and efficacy data 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 preferred shares. Through December 31, 2017, we had received gross proceeds of $135.3 million from sales of our 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 and $39.7 million for the years ended December 31, 2016 and 2017, respectively. As of December 31, 2017, we had an accumulated deficit of $59.4 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. In addition, GSK novated to us their R&D and collaboration and license 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 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. 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, and we issued to GSK 15,563,230 Series B-2 preferred shares.

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 alterative 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. 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 the expected future sales. See Note 14 to our consolidated financial statements appearing at the end of this prospectus for additional details of the GSK Agreement and the expected 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 preferred shares

In August 2018, we received gross cash proceeds of approximately $150.0 million from the sale of our Series C preferred shares. See "— Liquidity and capital resources."

Components of our results of operations

Revenue

Since inception through December 31, 2017, we had not generated any revenue from product sales. 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.

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 at 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 expect to recognize a significant charge to research and development expense related to the acquisition of in-process research and development programs that have no future alternative use. See Note 14 to our consolidated financial statements appearing at the end of this prospectus for additional details of the GSK Agreement and its expected 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 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 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 United Kingdom corporate taxation. 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 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.

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. 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

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 income (expense):			
Interest income	3	—	(3)
Change in fair value of tranche obligations	289	—	(289)
Other income (expense), net	(154)	(1,179)	(1,025)
Total other income (expense)	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)

Comparison of the years ended December 31, 2016 and 2017

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 $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 approximately $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 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.

Liquidity and capital resources

From our inception through December 2017, 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 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 December 31, 2017, we had received gross proceeds of $135.3 million from sales of preferred shares and reimbursement of $6.2 million from our subcontract agreement with UCLA. As of December 31, 2017, we had cash of $89.9 million. In August 2018, we received gross cash proceeds of approximately $150.0 million from the sale of our Series C 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,	
	2016	2017
	(in thousands)	
Net cash used in operating activities	$ (14,566)	$ (32,487)
Net cash used in investing activities	(190)	(1,559)
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

Operating activities

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 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 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 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 preferred shares in January 2017 and $107.1 million of net proceeds from the sale of our Series B 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

through . 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 169,615 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 a non-refundable royalty on annual sales of each of the product candidates that receives marketing approval, and milestone payments up to an aggregate of £90.0 million for OTL-200 and OTL-300 based on achievement of certain sales milestones. For example, our royalty obligations for OTL-101 for ADA-SCID are a flat mid-single digit percentage. Our royalty obligations for OTL-103 for WAS and OTL-200 for MLD are tiered starting at a percentage in the mid-teens and our royalty obligations for OTL-300 for TDBT are tiered from high-single digit to low double-digit percentages. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. Our royalty obligations with respect to OTL-200 and OTL-103 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. 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.

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 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 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 preferred shares. We determine the fair value per share of the underlying preferred shares by taking into consideration our most recent sales of our 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 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 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 and $2.97 per share as of October 31, 2017. 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 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 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 December 31, 2017, 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:

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]	372,500	£ 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

(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 and October 26, 2017, 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 and $2.97 per share, as presented, in connection with a retrospective fair value assessment for financial reporting purposes.

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. 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.

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, our tax incentive receivable from the U.K. government was $0.1 million and $0.9 million, respectively. These amounts have not yet been received from the HMRC.

Quantitative and qualitative disclosures about market risks

Interest rate sensitivity

As of December 31, 2017, we had cash of $89.9 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 December 31, 2017, 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, which 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

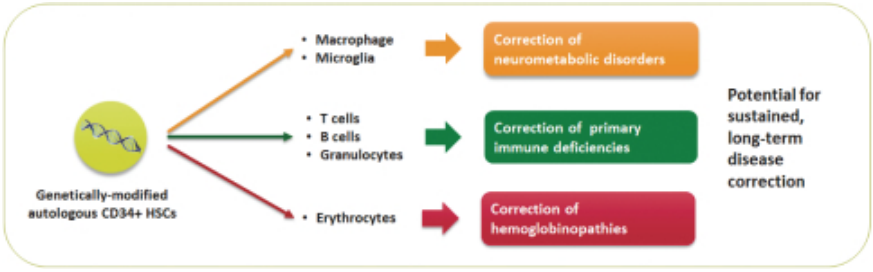
We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, HSCs into a gene-modified 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 140 patients across five different diseases and have accumulated compelling durable efficacy and safety data. 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 regulatory submissions for approval of up to three of our most advanced clinical-stage product candidate in the next three years. 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.

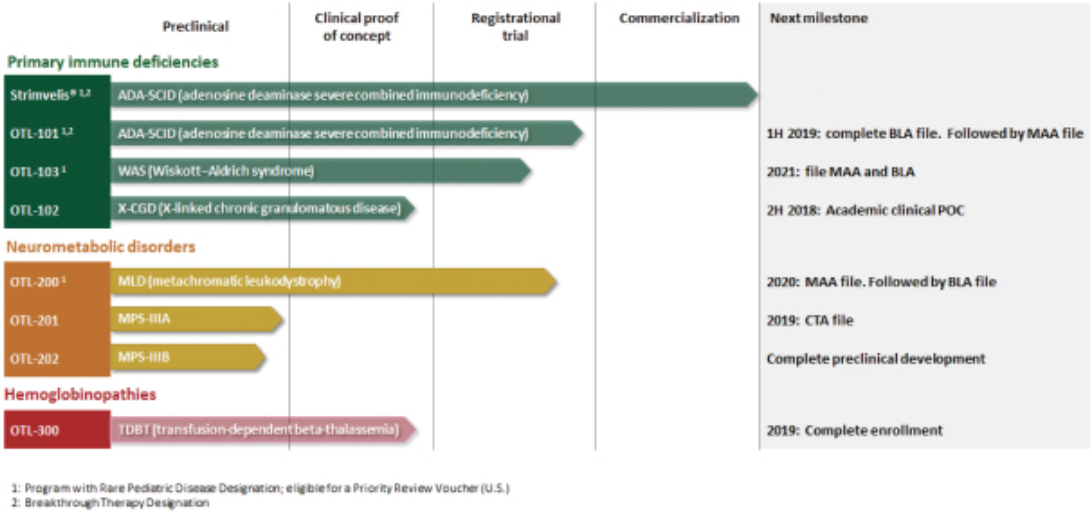
We intend to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. The indications we are initially targeting in our primary immune deficiencies and neurometabolic franchises (ADA-SCID, MLD, WAS, X-CGD, and MPS-IIIA) alone have a combined annual incidence 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 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. In addition, we believe our long-term clinical follow-up across multiple diseases and with vectors carrying different genes supports the safety of our autologous *ex vivo* gene therapy approach. This stands in contrast to the current standard of care for many of the diseases that we are initially targeting, where the use of allogeneic, or donor, HSC transplantation, or HSCT, carries a significant risk of complications and mortality, and other treatment options such as chronic ERT have limited efficacy.

We have a broad and advanced portfolio of wholly-owned commercial and development stage products and product candidates. We currently anticipate filing one product for regulatory approval in each of the next three years.



Three of our clinical-stage product candidates are currently in registrational trials and have shown compelling efficacy and safety data:

- OTL-101 is our product candidate for ADA-SCID, a rare, life-threatening inherited disease of the immune system. Drug product has been administered in 61 patients with a follow-up of up to six years post-treatment. The combined data from our two principal trials indicate overall survival of 100% with event-free survival of 97%. We expect to initiate a rolling BLA for OTL-101 with the FDA during the second half of 2018 and to complete submission during the first half of 2019, followed by an MAA submission with the EMA. 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.

- OTL-200 is our product candidate for MLD, a rare and rapidly progressive neurometabolic disorder. OTL-200 has evidenced sustained expression of the deficient ARSA enzyme, with significant long-term motor and cognitive improvements in most patients. These results exhibit the ability of our approach to target complex diseases which involve the central nervous system. There are no approved therapies for treatment of MLD available today. We plan to submit an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA.
- 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 achieved an overall survival of 100% in eight patients with a follow-up of up to eight-years post-treatment, with clinically meaningful reductions in bleeding events and infections observed at three years. We plan to submit an MAA with the EMA and a BLA with the FDA for OTL-103 in 2021.

Beyond these three lead product candidates, our other clinical-stage programs, OTL-102 for X-CGD and OTL-300 for TDBT continue to generate favorable safety and efficacy data in initial clinical trials. We are also expanding our neurometabolic disorder 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 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 number of patients treated and maximum survival follow-up as of July 2018 across the lead programs in our franchise areas.

Franchise	Program	Patients Treated [1]	Maximum survival follow-up
Primary immune deficiencies	**OTL-101** (ADA-SCID)	61	~6 years
	Strimvelis® (ADA-SCID)	24	~18 years
	OTL-103 (WAS)	15	~8 years
	OTL-102 (X-CGD)	10	~3 years
Neurometabolic disorders	**OTL-200** (MLD)	30	~8 years
Hemoglobinopathies	**OTL-300** (TDBT)	9	~3 years
Total		149 patients	

(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.

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.

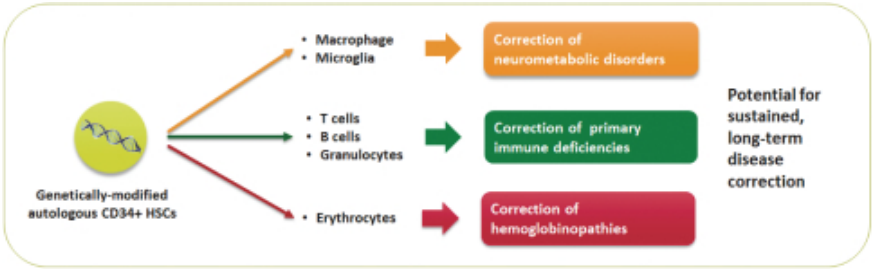
We have global commercial rights to Strimvelis and all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe, subject to obtaining necessary marketing approvals in those jurisdictions. We plan to deploy a focused 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

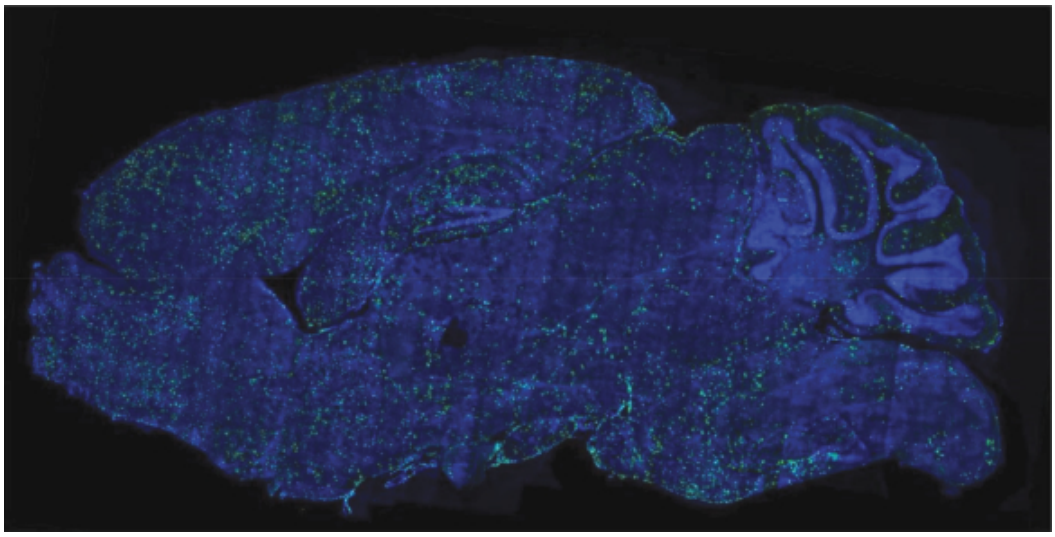
Our *ex vivo* gene therapy approach seeks to transform a patient's autologous HSCs into a gene-modified drug product to treat the patient's disease. HSCs are self-renewing cells that are capable of differentiating into all types of blood cells, including white blood cells, red blood cells and platelets. 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.

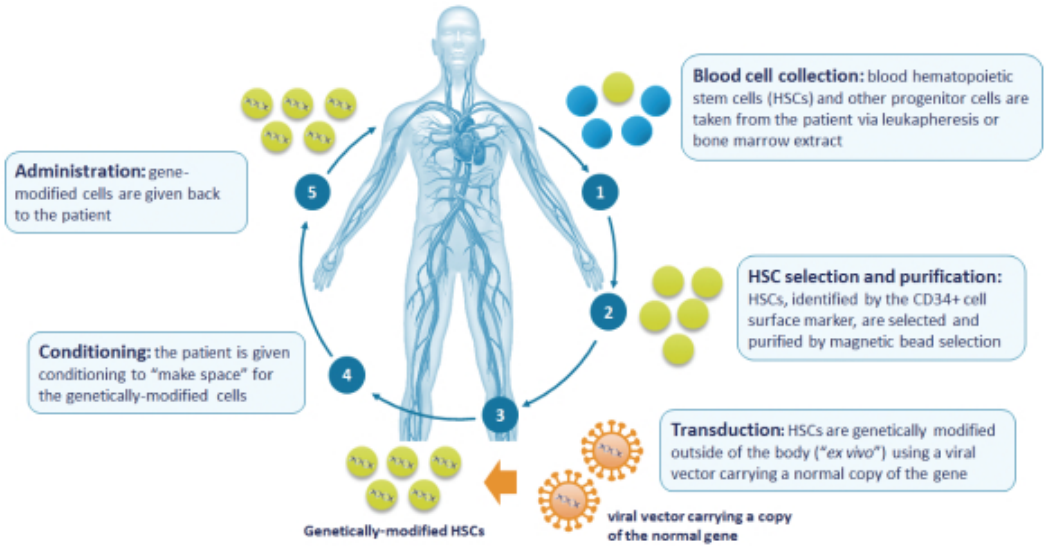
Transgene distribution in brain of mouse model following administration of HSCs transduced with GFP encoding vector



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.

Certain of our clinical-stage product candidates have been evaluated in registrational trials to date using fresh product formulation and/or drug product derived from HSCs extracted from the patients' bone marrow only. 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, as well as between drug product that has been cryopreserved and fresh drug product. We also plan to demonstrate comparability between vector and drug product manufactured by our selected third party CMOs with vector and drug product manufactured at the academic centers that have conducted certain of our clinical trials to date.

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 benefit to patients:** Durable and sustained clinical benefit 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 a favorable safety profile 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 140 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 140 patients, 125 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:

- **Rapidly 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 initiate a rolling BLA with the FDA for our product candidate OTL-101 for ADA-SCID during the second half of 2018 and to complete the submission in the first half of 2019, 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. We plan to file an MAA for our product candidate OTL-200 with the EMA in 2020, followed by a BLA with the FDA, and we intend to file 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 generate safety and efficacy data in initial clinical trials, and, assuming these trials are successful, we plan to rapidly progress these programs through clinical development to regulatory filing.
- **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.

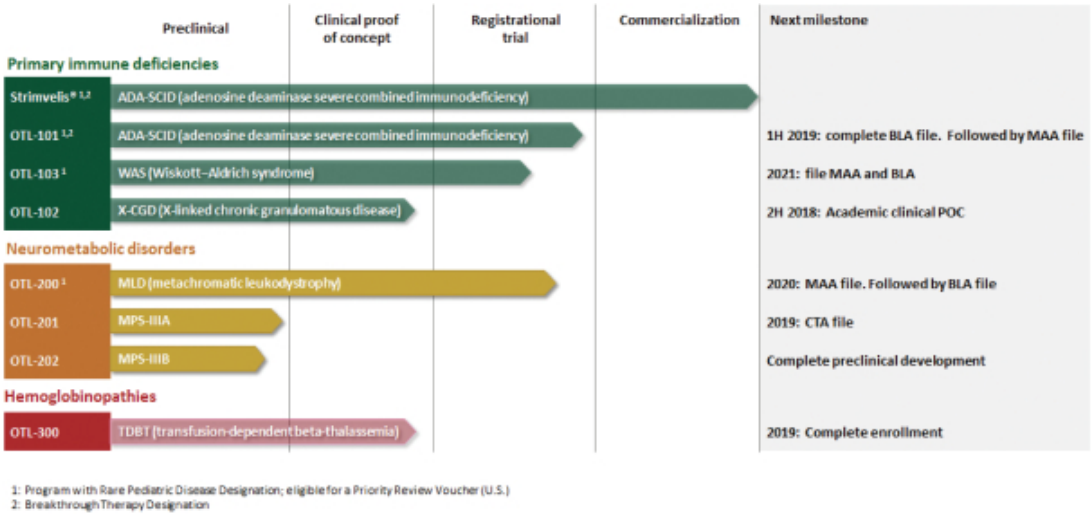
We seek to leverage our academic collaborations and focus our preclinical and clinical research on rare disease indications with high unmet need and for which we believe there is a high probability of clinical success, based on the results observed in our clinical trials to date. For example, we are 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 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 140 patients have been treated as of July 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:



Gene therapy for 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 is currently estimated to range from one in 200,000 to 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, or PEG-ADA, 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. Enrollment in the clinical trials supporting our marketing authorization applications is complete and follow-up in all clinical trials is ongoing. As of July 2018, 61 patients have been treated with drug product, with a maximum survival follow-up of up to approximately six years post treatment. Of these 61 patients, clinical data from a total of 30 patients is reflected in the summaries below. Based on our discussions with the FDA, we expect our BLA submission to include data from our UCLA registrational trial of 20 patients treated with a fresh product formulation, supportive data derived from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, supportive data derived from five patients treated with a cryopreserved formulation at UCLA, and any other patients with adequate follow-up at the time of submission. The remaining 26 patients treated as of July 2018 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this prospectus.

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 UCL Business plc, or 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 from the EMA for the treatment of ADA-SCID and a Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA. We expect to initiate a rolling BLA for OTL-101 with the FDA during the second half of 2018 and to complete submission in the first half of 2019, followed by an MAA submission with the EMA.

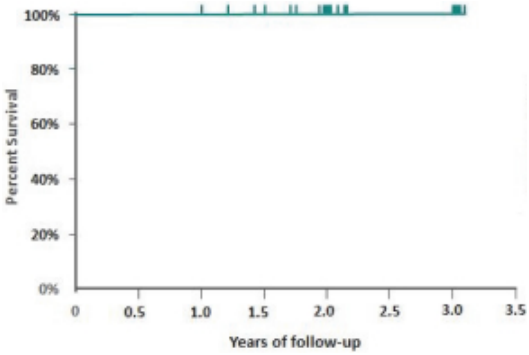
Ongoing registrational and supportive clinical trials

OTL-101 is being 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 investigator-sponsored supportive 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.

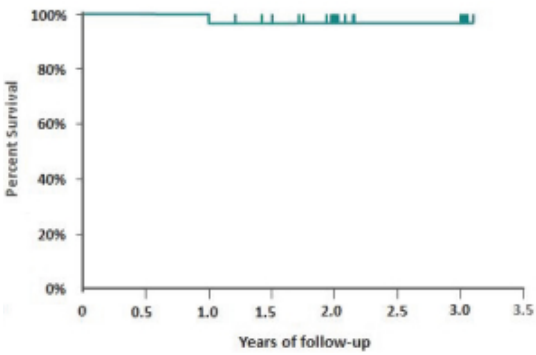
The combined data from the UCLA and GOSH clinical trials of the fresh formulation drug product demonstrate overall survival of 100% in a combined 30 patients, with event-free survival of 97%, defined as patient survival without the need for a rescue HSCT or the resumption of chronic ERT.

Overall Survival and event-free survival rates post-treatment in combined UCLA and GOSH ADA-SCID patient populations[(1)]

ADA-SCID: 100% Overall Survival
(30 patients out of 30)



ADA-SCID: 97% Event-free Survival
(29 patients out of 30)



(1) UCLA data as of March 2017; GOSH data as of April 2017.

Registrational trial at UCLA

Our anticipated rolling BLA submission for OTL-101 will be supported by data from 20 currently enrolled and treated patients in a registrational trial at UCLA for which follow-up is ongoing. 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 are 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 include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates.

Overall survival and event-free survival of 100% have been observed at 12 months post-treatment as of April 2017, the date of the most recent interim data report available to us, with none of the enrolled patients requiring 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. 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 of April 2018, safety data from the 20 patients treated in this clinical trial indicate that OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis in follow-ups ranging from 12.2 months to 26 months. There were 31 serious adverse events, or SAEs, reported, 14 of which were assessed by the investigator as being possibly related to protocol treatment or procedures. 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 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.

Supportive trial with GOSH

In a clinical trial being conducted by GOSH to support the registrational trial for OTL-101, as of July 2018, 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 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 March 2017, the date of the most recent interim data report available to us, 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 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. 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.

As of April 2018, the date of the most recent safety report available to us, safety data from the 10 patients treated in this clinical trial indicate that the investigational drug product was generally well-tolerated, with no instances of insertional mutagenesis up to six years post-treatment. There were 23 SAEs reported, one of which was assessed by the investigator as being possibly related to protocol treatment or procedures. The most common SAEs were pyrexia, infections and abnormal blood samples. 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.

Ongoing clinical trial with UCLA (with cryopreserved formulation)

We are also conducting a clinical trial at UCLA using a cryopreserved formulation of OTL-101 (with bone marrow as the cellular source), the primary aim of which is to support comparability of the fresh product formulation with the cryopreserved formulation of OTL-101. We intend to measure ADA activity, VCN and T-cell levels at six months post-treatment and compare those with the results obtained from our registrational trial with fresh product formulation. We expect to use these data to support the *in vitro* comparability analysis that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively. Preliminary data from five evaluable patients treated with our cryopreserved formulation of OTL-101 suggest that this formulation is comparable to the fresh formulation of OTL-101. We are continuing to evaluate the data from this ongoing trial and anticipate that this data will be used to support our BLA and MAA submissions.

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 arylsulfatase-A, or 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

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 early juvenile MLD, representing approximately 30% 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 late juvenile and adult MLD, representing approximately 10% 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 approximately one in 100,000 live births in the United States and up to 2.8 in 100,000 live births in Europe.

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 May 3, 2017, we have evaluated OTL-200 in a total of 30 patients, with a maximum survival follow-up of up to approximately eight years post treatment, comprised of 20 patients in our registrational trial with a fresh product formulation, one patient 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 halt or slow the disease progression and 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 from the EMA for the treatment of MLD and a Breakthrough Therapy Designation from the FDA. OTL-200 has also received a Rare Pediatric Disease Designation from the FDA. We plan to file an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA.

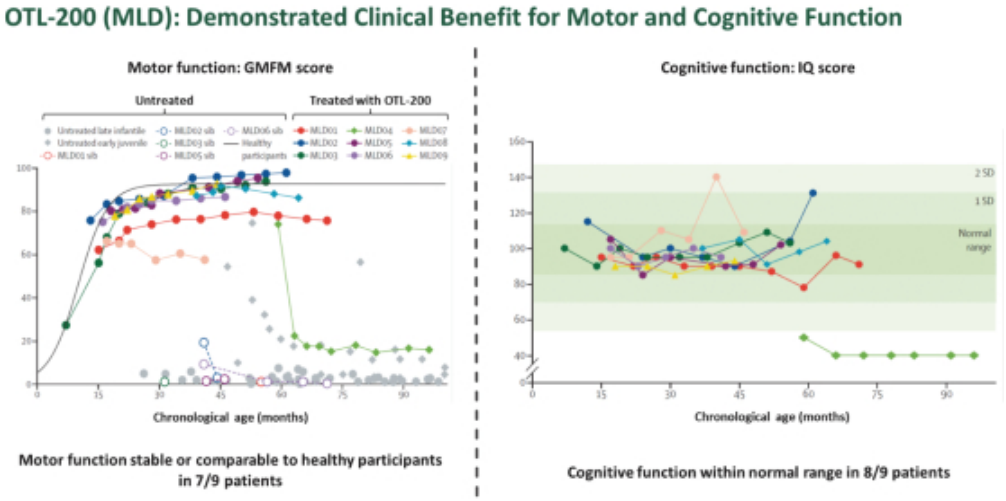
Registrational trial

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 addition to the 20 patients treated with OTL-200 in this clinical trial, nine patients were treated under a compassionate use program at San Raffaele Hospital, which followed the same protocol as that used in the clinical trial. Production 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.

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.

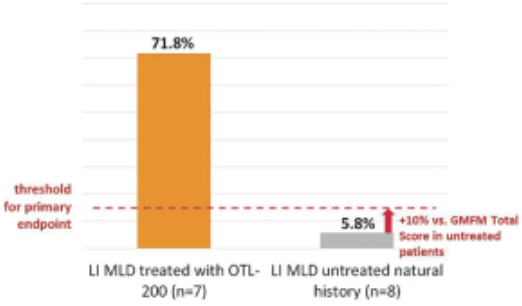
In this interim analysis, eight patients treated with OTL-200, seven of whom received treatment when pre-symptomatic, had prevention of disease onset or halted disease progression, as compared with patients in the natural history group, most of whom experienced rapid disease progression. In addition, GMFM scores 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).



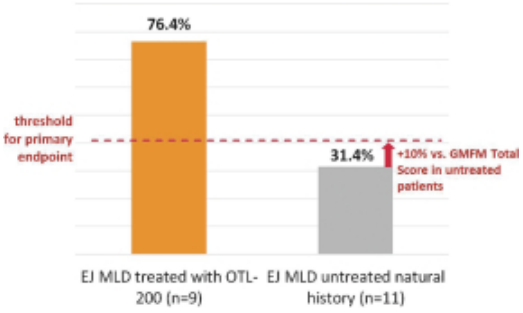
Presented below are efficacy data from an interim analysis of all 20 patients treated in this clinical trial as of December 2017, the date of the most recent interim efficacy data report available to us. Motor function was measured in this trial with a gross motor function measure score, or GMFM score, 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. Significant 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. 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, with a maximum survival follow-up of up to approximately eight years and a median follow-up of 2.4 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. Safety data 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 protocol treatment or procedures. The most common SAEs were motor dysfunction, dysphagia and infections. 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 the 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 the clinical trial of any SUSAR. In addition, as of March 2018, nine patients were treated under compassionate use program, all of whom are alive; six SAEs were reported, none of which were assessed by the investigator to be related to the drug product.

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 one patient enrolled as of July 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 data to support the comparability analyses that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively.

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 one in 200,000 live births worldwide.

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 July 2018, eight patients have been treated with OTL-103 in an ongoing registrational trial and seven additional patients in a compassionate use program, have been treated with OTL-103, with a maximum survival 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 we expect will be transferred to us by the end of 2018.

OTL-103 has received orphan drug designation from the FDA and from the EMA for the treatment of WAS and a Breakthrough Therapy Designation from the FDA. 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 be supported by 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. Production 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 seven 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.

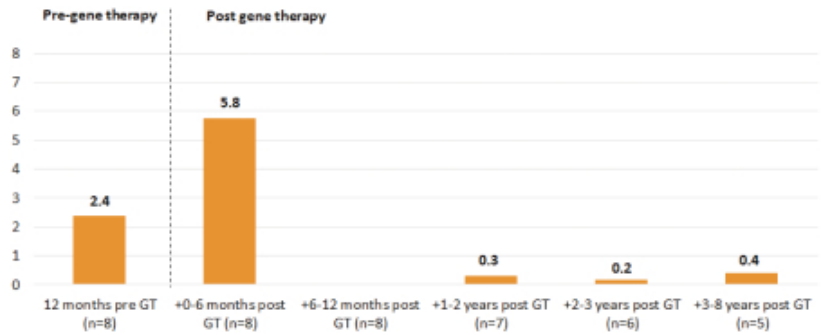
Patients treated in the registrational trial and compassionate use program were below the age of 12 years with a diagnosis of severe, classical WAS and were ineligible for HSCT treatment due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

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. 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

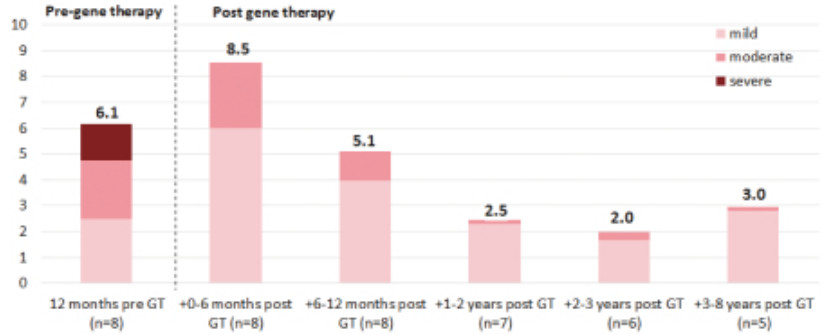
Severe infections per person/year



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 patients treated in the clinical trial, with a maximum survival follow-up of up to approximately eight years and a median follow-up of approximately 5.5 years. Safety data from the eight patients treated in this trial indicate OTL-103 was generally well-tolerated, with no instances of insertional mutagenesis up to eight years post-treatment. As of March 2018, all patients in the registrational study were alive. There were 29 SAEs reported, none of which were assessed by the investigator as being possibly related to protocol treatment or procedures. The most common SAEs were infections, electrolyte imbalance, food allergy and neutropenia. 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. As of March 15, 2018, six SAEs were reported in seven patients treated under compassionate use. One of these patients died as a consequence of a pre-existing neurological disease. The event was deemed to be unrelated to the product. All the other 6 compassionate use patients are alive.

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 one in 200,000 live births in the United States.

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 a license agreement with Généthon.

OTL-102 has received orphan drug designation from the EMA for the treatment of X-CGD.

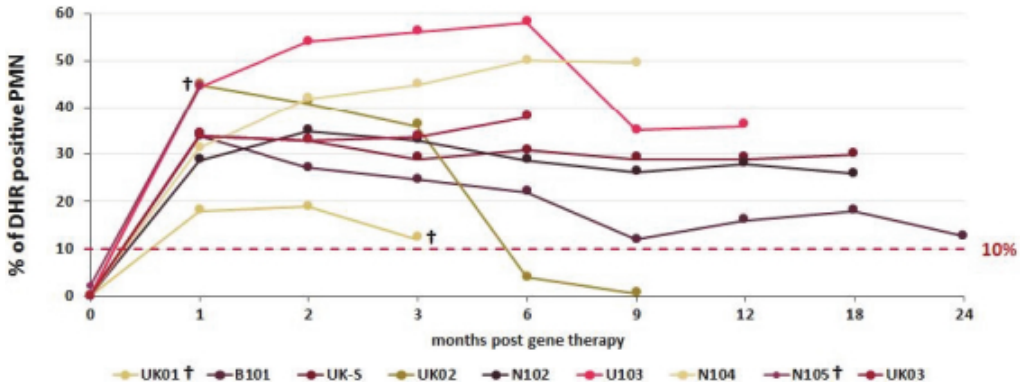
Ongoing clinical trials

OTL-102 is currently being investigated in two ongoing investigator-sponsored 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. As of January 2018, five patients have been treated in the clinical trial in the United States, and three patients have been treated in the clinical trial in Europe, in each case with a fresh product formulation. Two patients have been treated in a compassionate use program in Europe with a fresh 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.

OTL-102: oxidase activity(1)
(percentage of DHR-positive peripheral mononuclear cells or PMN)



(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 60,000 symptomatic individuals born each year and a global prevalence of more than 200,000 patients.

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.

Ongoing clinical trials (cryopreserved formulation)

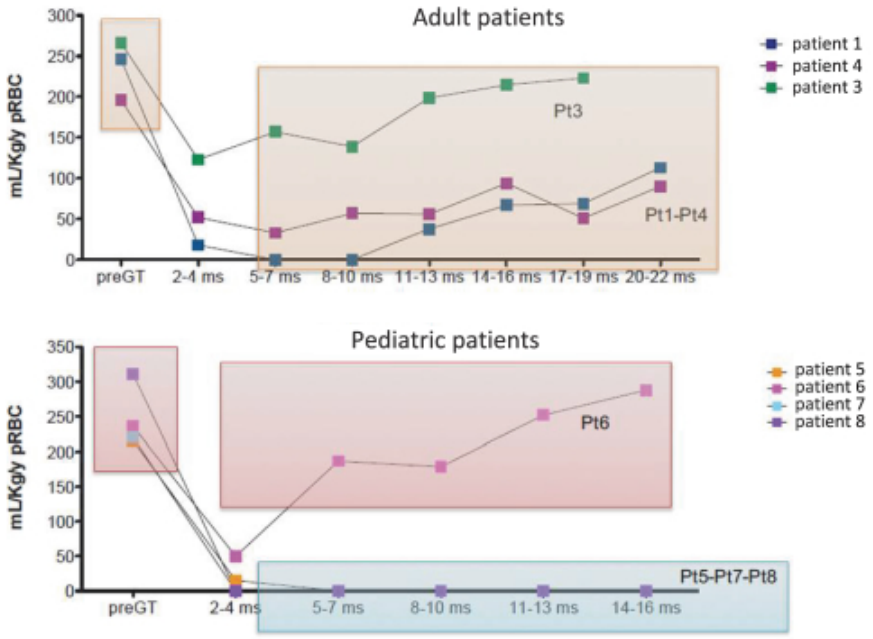
OTL-300 is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The target enrollment in this trial is 10 patients with TDBT, and as of July 2018, nine patients have received a single dose of a cryopreserved 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.

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 possibly related to protocol treatment or procedures. 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 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.

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. Life expectancy for patients with MPS-IIIA and MPS-IIIB is between 10 to 25 years and 15 to 30 years, 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 an effective treatment option 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.

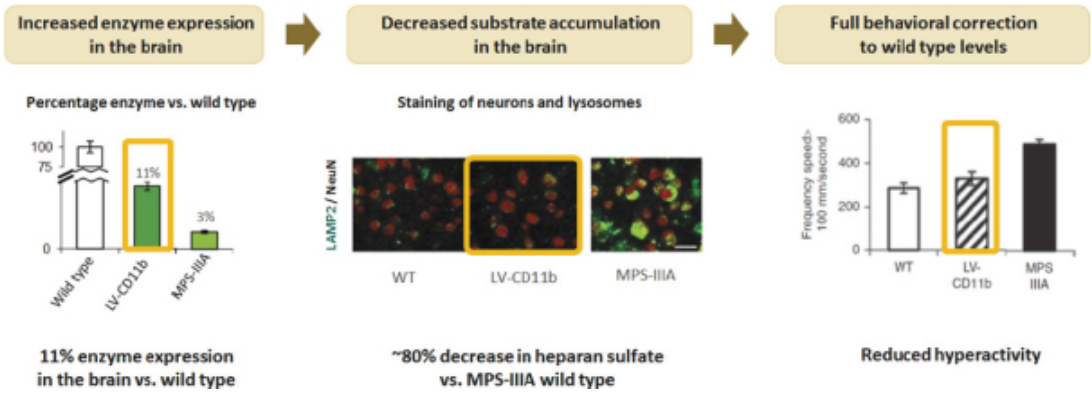
Preclinical studies

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.

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 U.S.

Patent and Trademark Office 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 Act 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 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 and collaboration and license 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 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 preferred shares.

Under the GSK Agreement we are also obligated to pay non-refundable royalties on sales of each of the product candidates that receive marketing approval, and milestone payments up to an aggregate of £90.0 million upon achievement of certain sales milestones. 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 beginning in the mid-teens 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 from the high single-digits to low double-digits for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. 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 terminate 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.

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 that certain research and development collaboration and license agreement, or the R&D Agreement, dated October 15, 2010, as amended, by and among GSK and 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. 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.

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 Phase I/II 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 Phase I/II clinical trials with autologous *ex vivo* lentiviral gene therapy. 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 Phase I/II clinical trial with autologous *ex vivo* lentiviral gene therapy in France, to which we have certain rights.
- **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, and that bluebird bio anticipates filing an MAA in a patient population with non ß0/ß0 TDBT with EMA in 2018. In addition, Memorial Sloane Kettering Cancer Center has been conducting a Phase I 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 Biologics License Application, or 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 CGMPs 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 is 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.

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.

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 human cells, tissues, and cellular and tissue based products 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 CGMPs 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 Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as 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 PPACA (or 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 a marketing authorization application. The application used to file 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 marketing authorization application 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 marketing authorization applications 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, Centers for Medicare and Medicaid Services, 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 PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as 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 July 23, 2018.

Name	Age	Position(s)
Executive Officers:		
Mark Rothera	55	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

(1) Dr. Pasteur has indicated to us his intention to resign from our board of directors immediately prior to the consummation of this offering.

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 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 consummation of this offering.

Charles A. Rowland, Jr. has served as 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.

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 nine members. Dr. Pasteur, currently a member of our board of directors, has indicated to us his intention to resign from our board of directors

upon the consummation of this offering. Our board of directors has determined that, of our nine 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."

Committees of our board of directors

Our board of directors has three standing committees: an audit committee, a remuneration committee and a nominating committee.

Audit committee

The audit committee consists of , and , and assists the board of directors in overseeing our accounting and financial reporting processes. will serve as chairman of the audit committee. The audit committee consists exclusively of members of our board who are financially literate, and 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.

Remuneration committee

The remuneration committee consists of , and . will serve as chairman of the remuneration committee. Under SEC and Nasdaq rules, there are heightened independence standards for members of the remuneration 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 remuneration committee members are expected to meet this heightened standard.

The remuneration 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 , and . 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 remuneration 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 Employee Share Option Plan, or the 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.

We reserved ordinary shares for issuance under the 2016 Plan, which includes ordinary shares reserved for issuance under our Non-Employee Sub-Plan described below. Our board may act to increase the number of ordinary shares available for issuance.

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.

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 on , 2018 and approved by our shareholders on , 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 remuneration 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 ordinary shares, or the Initial Limit, for the issuance of awards under the 2018 Plan, plus the ordinary shares remaining available for issuance under our 2016 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 % of the outstanding number of ordinary shares on the immediately preceding December 31, or

such lesser number of shares as determined by our remuneration 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.

Share options and share appreciation rights with respect to no more than ordinary shares may be granted to any one individual in any one calendar year. 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 ordinary shares.

The 2018 Plan will be administered by our remuneration committee. Our remuneration 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 remuneration 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 remuneration 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 remuneration committee and may not exceed 10 years from the date of grant. Our remuneration committee will determine at what time or times each option may be exercised.

Our remuneration 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 remuneration 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 remuneration 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 remuneration 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 remuneration 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 remuneration 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 on , 2018 and approved by our shareholders on , 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 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) % of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 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 days of employment and whose customary employment is for more than 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 remuneration committee, offerings will usually begin on each January 1 and July 1 and will continue for six-month periods, referred to as offering periods. 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 % 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 may purchase no more than $ worth of ordinary shares, valued at the start of the purchase period, under the ESPP in any calendar year.

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.

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 research and development and collaboration and license 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 preferred shares. Under the GSK Agreement we are also obligated to pay non-refundable royalties on sales of each of the product candidates that receive marketing approval, and milestone payments up to an aggregate of £90.0 million based upon achievement of certain sales milestones. 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 beginning in the mid-teens 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 from the high single-digits to low double-digits 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. 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.

Subscription of our Series A 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 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 preferred shares by related persons:

Shareholder	Series A 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 preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 10,000,000 shares of Series A 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 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 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 preferred shares by related persons:

Shareholder	Series B 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 preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 1,500,000 shares of Series B 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 preferred shares

In August 2018, we sold an aggregate of 17,421,600 shares of our Series C 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 preferred shares by related persons:

Shareholder	Series C 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 preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,613,240 shares of Series C preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,613,240 shares of Series C 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 preferred shares, we entered into subscription and shareholder agreements containing registration rights and information rights, among other things, with certain holders of our 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 party transactions policy

Prior to the completion of this offering, we intend to adopt a related party transactions policy.

Principal shareholders

The following table sets forth information with respect to the beneficial ownership of Orchard Therapeutics Limited's ordinary shares as of , 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 , 2018. Percentage ownership calculations are based on ordinary shares outstanding as of , 2018, after giving effect to the conversion of all of our preferred shares into ordinary shares on a one-for-one basis and our corporate reorganization as described elsewhere in this prospectus.

The percentage of shares beneficially owned after completion of this offering is based on ordinary shares outstanding after this offering, including ordinary shares in the form of ADSs issued in connection with this offering.

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 , ordinary shares, representing of our issued and outstanding shares, were held by 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)	25,500,001		
GSK(2)	15,563,230		
Entities affiliated with Deerfield Management Company(3)	5,807,200		
Scottish Mortgage Investment Trust plc(4)	4,871,080		
Executive Officers and Directors:			
Mark Rothera(5)	572,884		
Frank E. Thomas(6)	11,614		
Bobby Gaspar, M.D., Ph.D.(7)	1,023,589		
James A. Geraghty(8)	42,973		
Joanne T. Beck, Ph.D.(9)	11,614		
Marc Dunoyer(10)	46,457		

Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
Jon Ellis, Ph.D.	—		
Alex Pasteur, Ph.D.	—		
Charles A. Rowland, Jr.(11)	11,614		
Hong Fang Song	—		
All current directors and executive officers as a group (10 persons)(12)	1,720,745		

* Represents beneficial ownership of less than one percent.

(1) Consists of (i) 1,250,000 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (ii) 10,000,001 of our ordinary shares issuable upon conversion of our Series A preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iii) 1,500,000 of our ordinary shares issuable upon conversion of our Series B preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iv) 1,250,000 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; (v) 10,000,000 shares of our ordinary shares issuable upon conversion of our Series A preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; and (vi) 1,500,000 of our ordinary shares issuable upon conversion of our Series B 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 15,563,230 of our ordinary shares issuable upon conversion of our Series B-2 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) 580,720 of our ordinary shares issuable upon conversion of our Series C preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,613,240 of our ordinary shares issuable upon conversion of our Series C preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,613,240 of our ordinary shares issuable upon conversion of our Series C 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) 4,000,000 of our ordinary shares issuable upon conversion of our Series B preferred shares and (ii) 871,080 of our ordinary shares issuable upon conversion of our Series C 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) 49,763 of our ordinary shares issuable upon conversion of our Series B preferred shares, (ii) 31,213 of our ordinary shares issuable upon conversion of our Series C preferred shares and (iii) 491,908 of our ordinary shares issuable upon exercise of options within 60 days of 2018.

(6) Consists of 11,614 of our ordinary shares issuable upon conversion of our Series C preferred shares.

(7) Consists of (i) 521,454 of our ordinary shares and (ii) 502,135 of our ordinary shares issuable upon exercise of options within 60 days of August 2, 2018.

(8) Consists of 42,973 of our ordinary shares issuable upon conversion of our Series C preferred shares.

(9) Consists of 11,614 of our ordinary shares issuable upon conversion of our Series C preferred shares.

(10) Consists of 46,457 of our ordinary shares issuable upon conversion of our Series C preferred shares.

(11) Consists of 11,614 of our ordinary shares issuable upon conversion of our Series C preferred shares.

(12) Consists of (i) 521,454 of our ordinary shares, (ii) 49,763 of our ordinary shares issuable upon conversion of our Series B preferred shares, (iii) 155,485 of our ordinary shares issuable upon conversion of our Series C preferred shares and (iv) 978,351 of our ordinary shares issuable upon exercise of options within 60 days of 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.

Following our corporate reorganization, certain resolutions will be required to be passed by our shareholders prior to the completion of this offering. These will 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 £ for a period of 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 August 2, 2018, the issued share capital of Orchard Therapeutics Limited was 11,793,356 ordinary shares and 75,182,984 preferred shares. The nominal value of our ordinary shares and preferred shares is £0.00001 per share and each issued ordinary share and preferred share is fully paid. The issued share capital consisted of 23,580,231 ordinary shares, 21,000,000 Series A preferred shares, 21,198,154 Series B preferred shares, 15,563,230 Series B-2 preferred shares and 17,421,600 Series C preferred shares. As of August 2, 2018, the issued share capital of Orchard Rx Limited was 1 ordinary share of £0.00001. Following the contemplated exchange of shares of Orchard Therapeutics Limited for shares of Orchard Rx Limited, the issued share capital of Orchard Rx Limited will be the same number of ordinary and preferred shares in the same classes. As of the completion of the corporate reorganization and this offering, in each case, assuming an initial public offering price of $ per ADS, the midpoint of the range set forth on the cover page of this prospectus, our issued share capital will be 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). On , 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). On , 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 shares of our ordinary shares issuable upon the conversion of our Series A, Series B, Series B-2 and Series C 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 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 shares of our ordinary shares issuable upon the conversion of 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 on 2018 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 in paragraph 3.3(a) and 3.3(b) above were included in the special resolution passed on 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 on 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 £ 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.

	England and Wales	Delaware
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 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.	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 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.

	England and Wales	Delaware
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 certain period, may themselves convene a general meeting.	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
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.

	England and Wales	Delaware
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 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.	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.
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.

	England and Wales	Delaware
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 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.	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 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.

	England and Wales	Delaware
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 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.	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
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 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

, or , has agreed to act as the depositary for the ADSs. depositary offices are located at , , . 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 , Branch, located at .

We have appointed 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- 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, ordinary shares that are 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.

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 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; or
- 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 securities 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 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 the 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 offer, 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 United States and England and Wales legal considerations 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); and
- the ordinary shares presented for deposit have not been stripped of any rights or entitlements.

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 United States and England and Wales considerations 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; and/or
- restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit.

The deposit agreement may not be modified to impair your right to withdraw the securities 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 securities represented by ADSs.

If the depositary timely receives voting instructions from a holder of ADSs, it will endeavor 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 held on deposit at that time 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 held on deposit 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 herein). 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 to whom the ADSs are issued (in the case of ADS issuances) and to the person whose 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 of the 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 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.

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.

Pre-release transactions

Subject to the terms and conditions of the deposit agreement, the depositary may issue to broker/dealers ADSs before receiving a deposit of ordinary shares or release ordinary shares to broker/dealers before receiving ADSs for cancellation. These transactions are commonly referred to as “pre-release transactions,” and are entered into between the depositary and the applicable

broker/dealer. The deposit agreement limits the aggregate size of pre-release transactions (not to exceed 30% of the ordinary shares on deposit in the aggregate) and imposes a number of conditions on such transactions (e.g., the need to receive collateral, the type of collateral required, the representations required from brokers, etc.). The depositary may retain the compensation received from the pre-release transactions.

Taxes

You will be responsible for the taxes and other governmental charges payable on the ADSs and the securities 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 and the ADRs 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) is governed by the laws of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, YOU WAIVE YOUR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT OR THE ADRs AGAINST US AND/OR THE DEPOSITARY.

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, we will have ADSs outstanding, representing 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 ADSs, or 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 the remaining 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 shares immediately after the closing of this offering based on the number of ordinary shares outstanding as of ; 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. 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. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares.

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).

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. 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 determine 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, our U.S. tax counsel expresses no opinion regarding our PFIC status.

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. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain; however, our CFC status for the current taxable year is uncertain and we may be a CFC for the current taxable year. 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	

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 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 $.

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 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 of 1933.

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 of 1933, 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 European Economic Area (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	$ *
Nasdaq Global Market listing fee	*
FINRA filing fee	*
Printing expenses	*
Legal fees and expenses	*
Accounting fees and expenses	*
Miscellaneous costs	*
Total	*

* To be completed by amendment.

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 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

	Page
Consolidated financial statements of Orchard Therapeutics Limited	
Report of independent registered public accounting firm	F-2
Consolidated balance sheets	F-3
Consolidated statements of operations and comprehensive loss	F-4
Consolidated statements of convertible preferred shares and shareholders' (deficit) equity	F-5
Consolidated statements of cash flows	F-6
Notes to consolidated financial statements	F-7

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

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

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

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.

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 (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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 preferred shares") were issued in three tranches. The Company was obligated to issue second and third tranches of Series A 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 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.

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,

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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 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 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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 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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The tranche obligations were settled when the respective second and third tranches of Series A 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

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Depreciation expense for the years ended December 31, 2016 and 2017 was $6,000 and $0.3 million, respectively.

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 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 preferred shares and 21,198,154 shares have been designated as Series B convertible preferred shares (the "Series B preferred shares").

Until September 2017, the Series A and Series B preferred shares (collectively, the "Preferred Shares") were classified in temporary equity as the 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 Preferred Shares while that holder controlled a majority of the Company's board of directors. The 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 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 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 preferred shares, the Notes of $0.9 million were converted into 654,000 Series A preferred shares at conversion price of £1.00.

Preferred share financings

In February 2016, the Company issued 6,666,667 Series A preferred shares at a price of £1.00 per share (the “Series A Original Issue Price”) of which 6,012,667 Series A preferred shares were issued for net proceeds of $8.5 million and 654,000 Series A preferred shares were issued in settlement of the Notes.

In May 2016, the Company issued and sold 333,333 Series A 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 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 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 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 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 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 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 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 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 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 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 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 preferred shares	21,000,000	21,000,000	$ 26,994	$ 28,337	21,000,000
Series B 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 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.

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 preferred shares issued at a price lower than Series A

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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 Preferred Shares, voting together as a single class on an as-if-converted to ordinary shares basis.

Dividends

The holders of the Series A preferred shares, Series B 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 preferred shares, Series B 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 preferred shares, and Series B 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 preferred share and Series B 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 preferred shares on a pro rata basis (as if the ordinary shares and the Preferred Shares constituted one class) as described in the Amended Articles, except if the per share amount for Series A and Series B 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 Preferred Shares.

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 Preferred Shares set forth above. Each ordinary share entitles the holder to one vote, together with the

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

holders of Preferred Shares, on all matters submitted to the shareholders for a vote. The holders of 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 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 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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.

Orchard Therapeutics Limited

Notes to 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 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.

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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. 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 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 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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 169,615 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 shares.

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.

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 maybe 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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
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 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).

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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.

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 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 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 GlaxoSmithKline plc (collectively “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”). The acquisition compliments 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 Beta-Thal;
- 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 will account 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 £101.4 million ($143.9 million as of date of acquisition), including the amounts described below, and transaction costs of £0.6 million ($0.8 million as of date of acquisition) have been allocated to in-process research and development based on their relative fair values of the underlying program in development. The acquired in-process research and development will be recorded to research and development expense in the six-month period ended June 30, 2018.

Under the GSK Agreement, the Company made an upfront payment of £10.0 million ($14.2 million at the acquisition date) and issued to GSK 15,563,230 Series B-2 convertible preferred shares of the Company valued at £65.8 million ($93.4 million at the acquisition date) and acquired inventory for consideration of £4.9 million ($6.9 million at the acquisition date). The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher (“PRV”) from the United States Food and Drug Administration for each of the programs for MLD, WAS and Beta-Thal and to transfer the first such PRV to GSK. 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 Beta-Thal. In the event that GSK does not exercise this option with

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

respect to 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. The GSK option related to the PRVs resulted in a derivative liability that will be recorded initially at a fair value of £9.2 million ($13.1 million at the acquisition date) and will subsequently be marked-to-market, with any changes in fair value being recorded in the statements of operations.

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 £10.9 million ($15.5 million at the acquisition date). This liability will be amortized over the remaining period of expected sales of Strimvelis as net to operating expenses.

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 starting beginning in the mid-teens 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. 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

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 preferred shares are similar to those of the 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 preferred shares at a price of $8.61 per share.

Table of Contents

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:

(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 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 June 2018, Orchard Therapeutics Limited issued 188,462 ordinary shares to one investor as consideration for satisfying a milestone under 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 preferred shares to two investors for aggregate consideration of approximately £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 preferred shares to 17 investors for aggregate consideration of approximately £85.2 million.

In April 2018, Orchard Therapeutics Limited issued an aggregate of 15,563,230 Series B-2 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 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 10,296,532 ordinary shares, with exercise prices ranging from £0.00001 to £5.68 per share, to employees and directors pursuant to the 2016 Plan. In May 2018, Orchard Therapeutics Limited issued 13,125 ordinary shares to one individual upon exercise of options for an aggregate purchase price of $25,593.75.

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 adopted prior to the effectiveness of this registration statement).
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 Equity Incentive Plan (to be adopted prior to the 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 executive officers.
10.7*#	Form of Deed of Indemnity between the registrant and each of its non-executive directors.
10.8	Lease Agreement, dated as of January 19, 2018, by and between the Registrant and New Connect Investments 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.

* To be filed by amendment.

# 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 U.S. Securities and Exchange Commission 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, 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 , 2018.

ORCHARD RX LIMITED

By: _____

Mark Rothera

President and Chief Executive Officer

KNOW ALL BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Mark Rothera and Frank E. Thomas, and each of them, his or her true and lawful agent, proxy and attorney-in-fact, with full power of substitution and resubstitution, for and in his or her name, place and stead, in any and all capacities, to (i) act on, sign and file with the Securities and Exchange Commission any and all amendments (including post-effective amendments) to this Registration Statement together with all schedules and exhibits thereto and any subsequent registration statement filed pursuant to Rule 462(b) under the Securities Act of 1933, as amended, together with all schedules and exhibits thereto, (ii) act on, sign and file such certificates, instruments, agreements and other documents as may be necessary or appropriate in connection therewith, (iii) act on and file any supplement to any prospectus included in this Registration Statement or any such amendment or any subsequent registration statement filed pursuant to Rule 462(b) under the Securities Act of 1933, as amended, and (iv) take any and all actions which may be necessary or appropriate to be done, as fully for all intents and purposes as he or she might or could do in person, hereby approving, ratifying and confirming all that such agent, proxy and attorney-in-fact or any of his or her substitutes may lawfully do or cause to be done by virtue thereof.

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
Mark Rothera	President, Chief Executive Officer and Director *(Principal Executive Officer)*	, 2018
Frank E. Thomas	Chief Financial Officer and Chief Business Officer *(Principal Financial Officer and Principal Accounting Officer)*	, 2018
James A. Geraghty	Chairman of the Board of Directors	, 2018
Joanne T. Beck, Ph.D.	Director	, 2018
Marc Dunoyer	Director	, 2018

Table of Contents

Signature	Title	Date
_____ Jon Ellis	Director	, 2018
_____ Bobby Gaspar, M.D., Ph.D.	Director	, 2018
_____ Alex Pasteur, Ph.D.	Director	, 2018
_____ Charles A. Rowland, Jr.	Director	, 2018
_____ Hong Fang Song	Director	, 2018

Cogency Global Inc.

By: _____ Authorized Representative in the United States , 2018
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

Clause		Page
1.	Interpretation	3
2.	Sale and Purchase of Assets and Grant of Licences	19
3.	Consideration	20
4.	Completion	21
5.	Post-Completion Obligations	21
6.	Apportionments	32
7.	Responsibility for Liabilities	33
8.	Accounts Receivable	33
9.	Business Contracts	34
10.	Employees	35
11.	Intellectual Property	36
12.	Priority Review Vouchers	39
13.	Records, Audit and Audit Disagreement	40
14.	Restrictive Covenants	41
15.	Warranties	42
16.	Announcements, Confidentiality and Return of Information	44
17.	Joint Transition Committee	46
18.	VAT, Set-Off and Withholding Tax	48
19.	Wrong Pockets	49
20.	Material Breach; Termination	51
21.	Human Biological Sample Management	53
22.	Miscellaneous	53
23.	Variation and Waiver	54
24.	Whole Agreement	54
25.	Default Interest	54
26.	Notices	55
27.	Costs	56
28.	Rights of Third Parties	56
29.	Continuing Effect	56
30.	Assignment, Subcontracting	56
31.	Currency Conversion	57
32.	Governing Law, Appointment of Expert and Submission to Jurisdiction	57
33.	Invalidity	59
34.	Governing Language	59

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**)

Exhibit 10.2

ORCHARD THERAPEUTICS LIMITED
EMPLOYEE SHARE OPTION PLAN
WITH
NON-EMPLOYEE SUB-PLAN
AND
US SUB-PLAN

ADOPTED BY THE BOARD ON 14 September 2016
APPROVED BY SHAREHOLDERS ON 29 March 2017
AMENDED BY THE BOARD ON 7 February 2018
AMENDED BY THE BOARD ON 25 May 2018

CONTENTS

CLAUSE

1.	Interpretation	1
2.	Grant of Options	3
3.	Exercise Condition	4
4.	Overall grant limits	5
5.	Exercise of Options	5
6.	Manner of exercise of Options	6
7.	Alternative Settlement on Option Exercise	7
8.	Termination of employment	7
9.	Lapse of Options	7
10.	Tax liabilities	8
11.	Relationship with employment contract	9
12.	Takeovers and liquidations	9
13.	Exchange of Options	11
14.	Variation of share capital	11
15.	Notices	12
16.	Administration and amendment	13
17.	Third party rights	13
18.	Data protection	13
19.	Governing law	14
20.	Jurisdiction	14

Rules of the Orchard Therapeutics Limited Employee Share Option Plan

1. INTERPRETATION

1.1 The following definitions and rules of interpretation apply in the Plan.

Acting in Concert: has the meaning given to it in the City Code on Takeovers and Mergers published by the Panel on Takeovers and Mergers.

Board: the board of directors of the Company or a committee of directors appointed by that board to carry out any of its functions under the Plan.

Business Day: a day other than a Saturday, Sunday or public holiday in England when banks in London are open for business.

Change of Control: the sale of any of the Shares (in one transaction or a series of transactions) that will result in the Offeror of those Shares and persons Acting in Concert with him together acquiring Control of the Company, except where the Offeror is a company and the shareholders of that company and the proportion of shares in that company held by each of them following completion of the sale are substantially the same as the shareholders and their shareholdings in the Company immediately before the sale.

Company: Orchard Therapeutics Limited incorporated and registered in England and Wales with number 09759506.

Control: has the meaning given in section 719 of ITEPA 2003.

Employee: an individual who is an employee of a Group Member.

Employer Company: for the purposes of rule 10 and the definition of Tax Liability, the Option Holder's employer or former employer as applicable.

Employer NICs: any secondary class 1 (employer) NICs (or any similar liability for social security contribution in any jurisdiction) that the Company or any employer (or former employer) of an Option Holder is liable to pay as a result of any Taxable Event (or which that person would be liable to pay in the absence of an election of the type referred to in rule 10.4) and that may be lawfully recovered from the Option Holder.

Exercise Condition: a condition that must be satisfied before an Option may be exercised, which complies with rule 3 and is specified in the Option Certificate under rule 2.3.

Exercise Notice: the exercise notice referred to in rule 6.1

Exercise Price: the price at which each Share subject to an Option may be acquired on the exercise of that Option, which (subject to rule 14(b)) if Shares are to be newly issued to satisfy the Option, may not be less than the nominal value of a Share.

Grant Date: the date on which an Option is granted under the Plan.

Group: the Company and its Subsidiaries (references to **Group Member** shall be construed accordingly).

ITEPA 2003: the Income Tax (Earnings and Pensions) Act 2003.

Market Value: the market value of a Share determined to the satisfaction of the Board in accordance with the applicable provisions of Part VIII of the UK Taxation of Chargeable Gains Act 1992.

Minimum Proportion: means the proportion of an Option that may become exercisable due to an event under rule 8 or rule 12, and that shall be 100% except that if the Option becomes exercisable before any Exercise Condition has been achieved the Board (acting fairly and reasonably) may adjust the Minimum Proportion to take account of the extent to which the Exercise Condition has been achieved at the date of the relevant event.

NICs: National Insurance contributions.

Offeror: the person who acquires control of the Company under a Change of Control.

Option: a right to acquire Shares granted under the Plan.

Option Certificate: a certificate setting out the terms of an Option, entered into under rule 2.3.

Option Holder: an individual who holds an Option or, where applicable, his personal representatives.

Personal Data: any personal information that could identify an Option Holder.

Plan: the employees' share scheme (as defined in section 1166 of the Companies Act 2006) constituted and governed by these rules, as amended from time to time.

Rollover Period: the period during which Options may be exchanged for options over shares in another company under rule 13.1.

Shares: £0.00001 ordinary shares in the Company (subject to rule 14).

Subsidiary: has the meaning given in section 1159 of the Companies Act 2006.

Summary Dismissal: termination of the contract between the Option Holder and the Company in circumstances which allow the Company to terminate without notice or pay in lieu of notice under the relevant contract.

Sufficient Shares: the smallest number of Shares that, when sold, produce an amount at least equal to the relevant Tax Liability (after deduction of brokerage and any other charges or taxes on the sale).

Taxable Event: any event or circumstance that gives rise to a liability for the Option Holder to pay income tax and NICs or either of them (or their equivalents in any jurisdiction):

(a) in respect of the Option, including its exercise, its assignment or surrender for consideration, or the receipt of any benefit in connection with it;

(b) in respect of any Shares (or other securities or assets):

  (i) earmarked or held to satisfy the Option;

  (ii) acquired on exercise of the Option;

  (iii) acquired as a result of holding the Option;

(iv) acquired in consideration of the assignment or surrender of the Option;

(c) in respect of any securities (or other assets) acquired or earmarked as a result of holding Shares (or other securities or assets) mentioned in (b);

(d) arising as a result of entering into an election under section 430 or 431 of ITEPA 2003; or

(e) in respect of any amount due under PAYE in respect of securities or assets within (a) to (c) above, including any failure by the Option Holder to make good such an amount within the time limit specified in section 222 of ITEPA 2003.

Tax Liability: the total of:

(a) any income tax and primary class 1 (employee) NICs (or their equivalents in any jurisdiction) for which any Employer Company is or may be liable to account (or reasonably believes it is or may be liable to account) as a result of any Taxable Event; and

(b) unless the Employer Company, or the Company on behalf of the Employer Company, directs otherwise under rule 10.5, any Employer NICs (or similar liability in another jurisdiction) that any Employer Company is, or may be, liable to pay (or reasonably believes it is or may be liable to pay) as a result of any Taxable Event and that can be recovered lawfully from the Option Holder.

1.2 Rule headings shall not affect the interpretation of the Plan.

1.3 Unless the context otherwise requires, words in the singular shall include the plural and in the plural shall include the singular.

1.4 Unless the context otherwise requires, a reference to one gender shall include a reference to the other genders.

1.5 A reference to a statute or statutory provision is a reference to it as amended, extended or re-enacted from time to time.

1.6 A reference to a statute or statutory provision shall include all subordinate legislation made from time to time under that statute or statutory provision.

1.7 A reference to writing or written includes fax and email.

1.8 Any obligation on a party not to do something includes an obligation not to allow that thing to be done.

1.9 References to rules are to the rules of the Plan.

1.10 Any words following the terms **including**, **include**, **in particular**, **for example** or any similar expression shall be construed as illustrative and shall not limit the sense of the words, description, definition, phrase or term preceding those terms.

2. GRANT OF OPTIONS

2.1 Subject to the rules, the Company (acting through the Board) may grant an Option to any Employee it chooses.

2.2 The Company may not grant Options at any time when that grant would be prohibited by, or in breach of, any law, or regulation with the force of law.

2.3 The Company shall grant an Option by resolution of the Board and execution of a deed poll or Option Certificate in a form approved by the Board. Each Option Certificate shall (without limitation):

(a) specify the Grant Date of the Option;

(b) specify the number and class of the Shares over which the Option is granted;

(c) specify the Exercise Price;

(d) specify any Exercise Condition;

(e) specify the date when the Option will lapse, assuming that the Option is not exercised earlier and no event occurs to cause the Option to lapse earlier. This date may not be later than the tenth anniversary of the Grant Date;

(f) include a statement that the Option is subject to these rules (which shall be incorporated in the Option Certificate by reference);

(g) include a summary of the Option Holder's obligations under rule 10.

2.4 No amount shall be paid by an Employee for the grant of an Option.

3. EXERCISE CONDITION

3.1 On the Grant Date of any Option, the Board may specify one or more appropriate Exercise Conditions for the Option. An Exercise Condition may be specified to apply only to part of an Option.

3.2 The Board may vary or waive any Exercise Condition, provided that any varied Exercise Condition shall be (in the reasonable opinion of the Board):

(a) a fairer measure of performance than the original Exercise Condition, as judged at the time of the variation, if the original Exercise Condition relates to a measure of performance; and

(b) no more difficult to satisfy than the original Exercise Condition was at the Grant Date.

3.3 The Board shall determine whether, and to what extent, Exercise Conditions have been satisfied. If the Board considers that an Exercise Condition has become incapable of being satisfied, in whole or in part, that Option, or the appropriate part of it, shall lapse forthwith.

3.4 If an Option is subject to any Exercise Condition, the Board shall notify the Option Holder within a reasonable time after the Board becomes aware of the relevant information:

(a) whether (and, if relevant, to what extent) the Exercise Condition has been satisfied;

(b) of any subsequent change in whether, or the extent to which, the Exercise Condition has been satisfied;

(c) when that Exercise Condition has become incapable of being satisfied, in whole or in part; and

(d) of any waiver or variation of that Exercise Condition under rule 3.2.

3.5 For the avoidance of doubt, rule 3.2 permits the Board to make a general waiver of Exercise Conditions:

(a) on cessation of employment;

(b) on the occurrence of any event permitting the exercise of Options under rule 12; or

(c) the release of Options in exchange for New Options under rule 13.

4. OVERALL GRANT LIMITS

4.1 The total number of Shares subject to the Plan shall be 4,700,000 or such other number agreed by the Board from time to time.

5. EXERCISE OF OPTIONS

5.1 Subject to rule 8 and rule 12:

(a) An Option Holder may not exercise an Option before the earliest date on which it may be exercised as set out in the Option Certificate.

(b) An Option Holder may not exercise an Option before any Exercise Condition relating to that Option has been satisfied.

5.2 An Option Holder may not exercise an Option at a time when its exercise is prohibited by, or would be a breach of, any law or regulation with the force of law or other rule, code or set of guidelines (such as a personal dealing code adopted by the Company).

5.3 Subject to rule 5.4, an Option Holder may not exercise an Option at any time:

(a) while disciplinary proceedings by any Group Member are underway against him; or

(b) while any Group Member is investigating his conduct and may as a result begin disciplinary proceedings; or

(c) while there is a breach of his employment contract that is a potentially fair reason for his dismissal; or

(d) while he is in breach of a fiduciary duty owed to any Group Member; or

(e) after he has ceased to be an Employee, if there was a breach of his employment contract or fiduciary duties that (in the reasonable opinion of the Board) would have prevented the exercise of the Option had the Company been aware (or fully aware) of that breach, and of which the Company was not aware (or not fully aware) until after both:

(i) his ceasing to be an Employee; and

(ii) the time (if any) when the Board decided to permit him to exercise his Option.

5.4 The Company shall not unfairly frustrate a valid exercise of the Option by the inappropriate application of any provision of rule 5.3.

5.5 The Option Holder may not exercise the Option unless he has complied with rule 10.2.

6. MANNER OF EXERCISE OF OPTIONS

6.1 An Option shall be exercised by the Option Holder giving a written exercise notice to the Company, as follows:

(a) setting out the number of Shares over which the Option Holder wishes to exercise the Option. If that number exceeds the number over which the Option may be validly exercised at the time, the Company shall:

(i) treat the Option as exercised only in respect of that lesser number; and

(ii) refund any excess amount paid to exercise the Option or meet any Tax Liability.

(b) using a form that the Board will approve.

6.2 Subject to rule 7 any Exercise Notice shall be accompanied by payment of an amount equal to the Exercise Price multiplied by the number of Shares specified in the notice.

6.3 The Exercise Notice shall:

(a) include the Option Holder's agreement to pay the Tax Liability in accordance with rule 10.2; and

(b) include a power of attorney as required by rule 10.7.

6.4 Any Exercise Notice shall be invalid:

(a) to the extent that it is inconsistent with the Option Holder's rights under these rules and the Option Certificate;

(b) if any of the requirements of rule 6.1 or rule 6.2 are not met; or

(c) if any payment referred to in rule 6.2 is made by a cheque that is not honoured on first presentation or that fails in any other manner to transfer the expected value to the Company.

The Company may permit the Option Holder to correct any defect referred to in rule 6.4(b) or rule 6.4(c) (but shall not be obliged to do so). The date of any corrected Exercise Notice shall be the date of the correction rather than the original notice date for all other purposes of the Plan.

6.5 The Company shall allot and issue Shares (or, as appropriate, procure their transfer) within 30 days after a valid Option exercise, subject to the other rules of the Plan.

6.6 Shares allotted and issued in satisfaction of the exercise of an Option shall rank equally in all respects with the other shares of the same class in issue at the date of allotment, except for any restriction or any rights determined by reference to a date before the date of allotment.

6.7 Shares transferred in satisfaction of the exercise of an Option shall be transferred free of any lien, charge or other security interest, other than any restriction, and with all rights attaching to them, other than any rights determined by reference to a date before the date of transfer.

6.8 If the Shares are listed or traded on any stock exchange, the Company shall apply to the appropriate body for any newly issued Shares allotted on exercise of an Option to be listed or admitted to trading on that exchange.

7. ALTERNATIVE SETTLEMENT ON OPTION EXERCISE

7.1 Instead of delivering the number of Shares specified in the relevant Exercise Notice, the Company (at its discretion) may settle any Option exercise by issuing to the Option Holder a number of Shares equal to the number of Shares given by dividing the Notional Profit by the Market Value of one Share derived from the Market Value used to calculate the Notional Profit.

7.2 If the number of Shares calculated under this rule 7 is not a whole number, that number may be rounded up to the nearest whole Share at the discretion of the Company, failing which the Option Holder shall also receive a cash amount equal to the amount by which the Notional Profit exceeds the total Market Value of the Shares delivered under this rule 7 (as determined using the Market Value of one Share derived from the Market Value used to calculate the Notional Profit).

7.3 For the purposes of rule 7.1 "**Notional Profit**" means the current Market Value of the number of Shares over which the Option is exercised, less the total Exercise Price that would have been payable on that exercise.

8. TERMINATION OF EMPLOYMENT

8.1 If an Option Holder dies, his personal representatives may exercise such proportion of his Option as the Board may specify (not being less than the Minimum Proportion measured at the date of death) during the period ending 12 months after his death.

8.2 An Option Holder who gives or receives notice of termination of employment or who ceases to be an Employee for any reason other than Summary Dismissal may exercise such proportion of his Option as the Board may specify (not being less than the Minimum Proportion measured at the cessation date) during the period of 90 days after ceasing to be an Employee and it shall lapse at the end of that period.

8.3 An Option Holder shall not be regarded as ceasing to be an Employee until he is no longer an employee or director of any Group Member.

9. LAPSE OF OPTIONS

9.1 An Option Holder may not transfer or assign, or have any charge or other security interest created over an Option (or any right arising under it). An Option shall lapse if the relevant Option Holder attempts to do any of those things. However, this rule does not prevent the transmission of an Option to an Option Holder's personal representatives on the death of the Option Holder.

9.2 An Option shall lapse on the earliest of the following:

(a) any attempted action by the Option Holder falling within rule 9.1;

(b) when the Board so decides in accordance with rule 3.3, to the extent that an Exercise Condition has become wholly or partly incapable of being met;

(c) any date on which the Option shall lapse, as specified in the Option Certificate;

(d) the first anniversary of the Option Holder's death;

(e) if rule 8.2 applies the earlier of the date 90 days after the Option Holder ceases to be an Employee or the date of the Summary Dismissal;

(f) if any part of rule 12 applies, the time specified for the lapse of the Option under that part of rule 12; or

(g) when the Option Holder becomes bankrupt under Part IX of the Insolvency Act 1986, applies for an interim order under Part VIII of the Insolvency Act 1986, proposes or makes a voluntary arrangement under Part VIII of the Insolvency Act 1986, takes similar steps or is similarly affected, under laws of any jurisdiction that correspond to those provisions of the Insolvency Act 1986.

9.3 Part of an Option shall lapse where rule 8 applies and the Board has determined that the Option may be exercised, but only in part.

10. TAX LIABILITIES

10.1 The Option Holder shall indemnify the Employer Company in respect of any Tax Liability.

10.2 An Option may not be exercised unless the Option Holder:

(a) agrees, in writing, to pay the Tax Liability to the Employer Company; and

(b) has made arrangements, satisfactory to the Employer Company or Company, to pay the Tax Liability.

10.3 If an Option Holder does not pay the Tax Liability within seven days of any Taxable Event, the Company or Employer Company, as appropriate, may:

(a) if the relevant Taxable Event is the exercise of the Option, and the Shares are readily saleable at the time, retain and sell such number of Shares on behalf of the Option Holder as is necessary to meet the Tax Liability, and any costs of sale; or

(b) deduct the amount of any Tax Liability from any payments of remuneration made to the Option Holder on or after the date on which the Tax Liability arose. However, in the case of NICs, the Employer Company may only withhold such amount as is permitted by the Social Security Contributions Regulations 2001 (SI 2001/1004).

The Option Holder's obligations under rule 10.1 shall not be affected by any failure of the Company or Employer Company to withhold shares or deduct from payments of remuneration under this rule 10.3.

10.4 At the request of the Employer Company at any time before exercise of the Option, the Option Holder must elect, to the extent permitted by law, and using a form approved by HM Revenue & Customs, that the whole or any part of the liability for employer NICs arising as a result of a Taxable Event shall be transferred to the Option Holder.

10.5 The Employer Company (or the Company on behalf of the Employer Company) may:

(a) on the Grant Date, direct that the Tax Liability shall not include Employer NICs; or

(b) at any time after the Grant Date, but before the Option is exercised, release the Option Holder from his obligations in respect of Employer NICs under this rule 10, so that Employer NICs do not form part of the Tax Liability.

10.6 At the request of the Employer Company (or the Company on behalf of the Employer Company) on or before the date of exercise of the Option, the Option Holder must enter into a joint election under section 431(1) or section 431(2) of ITEPA 2003, in respect of the Shares to be acquired on exercise of the relevant Option.

10.7 The Exercise Notice may include a power of attorney appointing the Company as the Option Holder's agent and attorney for the purposes of rule 10.3 and rule 10.6.

11. RELATIONSHIP WITH EMPLOYMENT CONTRACT

11.1 The rights and obligations of any Option Holder under the terms of his office or employment with any Group Member or former Group Member shall not be affected by being an Option Holder.

11.2 The value of any benefit realised under the Plan by Option Holders shall not be taken into account in determining any pension or similar entitlements.

11.3 Option Holders and Employees shall have no rights to compensation or damages on account of any loss in respect of Options where this loss arises (or is claimed to arise), in whole or in part, from:

(a) termination of office or employment with; or

(b) notice to terminate office or employment given by or to,

any Group Member or any former Group Member. This exclusion of liability shall apply however termination of office or employment, or the giving of notice, is caused, and however compensation or damages are claimed.

11.4 Option Holders and Employees shall have no rights to compensation or damages from any Group Member or any former Group Member on account of any loss in respect of Options where this loss arises (or is claimed to arise), in whole or in part, from:

(a) any company ceasing to be a Group Member; or

(b) the transfer of any business from a Group Member to any person that is not a Group Member.

This exclusion of liability shall apply however the change of status of the relevant Group Member, or the transfer of the relevant business, is caused, and however compensation or damages are claimed.

11.5 An Employee shall not have any right to receive Options, whether or not he has previously been granted any.

12. TAKEOVERS AND LIQUIDATIONS

12.1 If the Board considers that a Change of Control is likely to occur, the Board may in its absolute discretion decide that the Option Holder may exercise all or any part of any Option within a reasonable period to be specified by the Board for that purpose and ending immediately before the Offeror obtains Control of the Company. The Board shall have discretion to determine what proportion (if any) of an Option shall be exercisable taking account of any matters as they think fit, provided that it shall not be less than the Minimum Proportion measured at the date of the Board's decision.

12.2 If a Change of Control occurs, the Option Holder may exercise such proportion of an Option as the Board may determine within 90 days after the time when the Offeror has obtained Control of the Company. The Board shall have discretion to determine what proportion (if any) of an Option shall be exercisable taking account of such matters as they think fit, provided that it shall not be less than the Minimum Proportion measured at the date of the Change of Control. Unless rule 12.3 applies, the Option shall lapse at the end of the 90 day period.

12.3 If a Change of Control occurs, an Option shall continue to exist if both the following conditions are met:

(a) the Offeror is a company;

(b) the Offeror declares within ten days following the time when the Offeror has obtained Control of the Company that it is willing to make an agreement for the exchange of Options under rule 13.1;

until the earlier of the following:

(c) the time when the Option Holder releases the Option under that exchange of options; and

(d) the latest date on which the Rollover Period expires,

when it shall lapse.

12.4 Any Option to which rule 12.3 applies shall not be capable of exercise under any rule of the Plan after it ceases to be capable of exercise under rule 12.2.

12.5 An Option Holder may exercise the Minimum Proportion of any Option during any period when any person is bound or entitled to acquire Shares under sections 979 to 982 or 983 to 985 of the Companies Act 2006. Any Option to which this rule 12.5 applies shall lapse at the later of:

(a) the end of the period during which that person is bound or entitled; and

(b) the time specified for the lapse of Options under rule 12.3, if it applies.

12.6 If any Shares, in one or a series of transactions, are sold or a right to acquire or dispose is granted resulting in the buyer or grantee and persons Acting in Concert with him together acquiring Control of the Company, but this does not constitute a Change of Control because the buyer is a company and its shareholders and the proportion of its shares held by each of them following completion of the sale are substantially the same as the shareholders and their shareholdings in the Company immediately before the sale, the Board shall use reasonable endeavours to make arrangements with the buyer as the Board, in its reasonable opinion, considers to be fair, for suitable replacement options under rule 13.1, or some other appropriate compensation to be offered to Option Holders.

If the Board is unable to make these arrangements with the buyer in 30 days after the buyer has acquired Control, then the provisions of rule 12.2 shall apply to the Options in the same way as if the sale had constituted a Change of Control.

12.7 Unless the relevant compromise or arrangement includes appropriate provisions that the Board considers to be fair in its reasonable opinion for:

(a) the replacement of Options; or

(b) other compensation for Option Holders for the loss of Options,

the Option Holder may exercise a proportion of his Option within six weeks after any person (in this rule 12.7, the **Controller**) obtains Control of the Company as a result of the court sanctioning a compromise or arrangement under section 899 of the Companies Act 2006. The Board shall have discretion to determine what proportion (if any) of an Option shall be exercisable taking account of these matters as they think fit, provided that the proportion shall not be less than the Minimum Proportion measured at the date of the court sanction.

12.8 Any Option to which rule 12.7 applies shall:

(a) if an exchange of options falling within is offered, continue to exist until the earlier of the following:

(i) the time when the Option is released under that exchange; and

(ii) the latest date on which the Rollover Period expires,

when it shall lapse.

Any Option to which this rule 12.8(a) applies shall not be capable of exercise under any other rule of the Plan after it ceases to be capable of exercise under rule 12.7.

(b) lapse at the end of the exercise period specified in rule 12.7 and rule 12.8(a) if such an exchange is not offered.

12.9 If a person, or group of persons Acting in Concert together, acquire Control of the Company by subscribing for new shares in the Company, the Board may in its absolute discretion decide to treat this as a Change of Control for all the purposes of the Plan.

12.10 In rule 12 and rule 13, a person shall be deemed to have obtained Control of a company if he, and others Acting in Concert with him, have obtained Control of it together.

12.11 If the shareholders of the Company receive notice of a resolution for the voluntary winding up of the Company, any Option Holder may exercise the Minimum Proportion of an Option at any time before that resolution is passed, conditional upon the passing of that resolution, and if the Option Holder does not exercise the Option, it shall lapse when the winding up begins.

12.12 The Board shall notify Option Holders of any event that is relevant to Options under this rule 12 within a reasonable period after the Board becomes aware of it.

13. EXCHANGE OF OPTIONS

13.1 A company that acquires Control of the Company may offer to grant a new option in exchange for an Option on terms that it considers appropriate. An Option Holder may accept such an offer within the applicable Rollover Period.

13.2 The Rollover Period shall be the period starting with the date the company acquires Control and ends on the earlier of:

(a) 90 days after that date; and

(b) where rule 12.7 applies, the date on which the person ceases to be bound or entitled to acquire Shares.

14. VARIATION OF SHARE CAPITAL

If there is any variation of the share capital of the Company (whether that variation is a capitalisation issue (other than a scrip dividend), rights issue, consolidation, subdivision or reduction of capital or otherwise) that affects (or may affect) the value of Options to Option Holders, the Board shall adjust the number and description of Shares subject to each Option or the Exercise Price of each Option in a manner that the Board, in its reasonable opinion, considers to be fair and appropriate. However:

(a) the total amount payable on the exercise of any Option in full shall not be increased; and

(b) the Exercise Price for a Share to be newly issued on the exercise of any Option shall not be reduced below its nominal value (unless the Board resolves to capitalise, from reserves, an amount equal to the amount by which the total nominal value of the relevant Shares exceeds the total adjusted Exercise Price, and to apply this amount to pay for the relevant Shares in full).

15. NOTICES

15.1 Except as maintained in rule 15.3, any notice or other communication given under or in connection with the Plan shall be in writing and shall be:

(a) delivered by hand or by pre-paid first-class post or other next working day delivery service at the **Appropriate Address**;

For the purposes of this rule 15, the Appropriate Address means:

(i) in the case of the Company, its registered office provided the notice is marked for the attention of the CEO;

(ii) in the case of an Option Holder, his home address; and

(iii) if the Option Holder has died, and notice of the appointment of personal representatives is given to the Company, any contact address specified in that notice.

(b) sent by fax to the fax number notified in writing by the recipient to the sender; or

(c) sent by email to the **Appropriate Email Address**.

For the purposes of this rule 15, Appropriate Email Address means:

(i) in the case of the Company, the email address of the CEO; and

(ii) in the case of the Option Holder, his work email address if he is permitted to access personal emails at work.

15.2 Any notice or other communication given under this rule 15 shall be deemed to have been received:

(a) if delivered by hand, on signature of a delivery receipt, or at the time the notice is left at the appropriate address;

(b) if sent by prepaid first-class post or other next working day delivery service, at 9.00 am on the second Business Day after posting, or at the time recorded by the delivery service;

(c) if sent by fax, at 9.00 am on the next Business Day after transmission; and

(d) if sent by email, at 9.00 am on the next Business Day after sending.

15.3 This rule does not apply to:

(a) the service of any notice of exercise under rule 6.1; and

(b) the service of any proceedings or other documents in any legal action or, where applicable, any arbitration or other method of dispute resolution.

16. ADMINISTRATION AND AMENDMENT

16.1 The Plan shall be administered by the Board.

16.2 The Board may amend the Plan from time to time, but no amendment may apply to Options granted before the amendment was made, except that each Option Holder may consent to the application to his Option of such an amendment.

16.3 The cost of establishing and operating the Plan shall be borne by the Group Members in proportions determined by the Board.

16.4 To satisfy the exercise of all the Options, the Company shall ensure that at all times:

(a) it has sufficient unissued or treasury Shares available, taking into account any other obligations of the Company to issue Shares and to transfer Shares from treasury, if the Company has restricted the number of Shares it can issue in its articles of association; and

(b) arrangements are in place for any third party to transfer issued Shares.

16.5 The Board shall determine any question of interpretation and settle any dispute arising under the Plan. In these matters, the Board's decision shall be final.

16.6 The Company shall not be obliged to notify any Option Holder if an Option is due to lapse.

16.7 The Company shall not be obliged to provide Option Holders with copies of any materials sent to the holders of Shares.

17. THIRD PARTY RIGHTS

17.1 A person who is not a party to an Option shall not have any rights under or in connection with it as a result of the Contracts (Rights of Third Parties) Act 1999 except where these rights arise under any rule of the Plan for any employer or former employer of the Option Holder that is not a party to an Option.

This does not affect any right or remedy of a third party that exists, or is available, apart from the Contracts (Rights of Third Parties) Act 1999.

17.2 The rights of the parties to an Option to surrender, terminate or rescind it, or agree any variation, waiver or settlement of it, are not subject to the consent of any person that is not a party to the Option as a result of the Contracts (Rights of Third Parties) Act 1999.

18. DATA PROTECTION

18.1 For the purpose of operating the Plan in the European Union, the Company will collect and process information relating to Option Holders in accordance with an appropriate privacy notice.

18.2 In all other jurisdictions, each Option Holder consents to the collection, holding, processing and transfer of his Personal Data by the Company or any Group Member for all purposes connected with the operation of the Plan.

18.3 The purposes of the Plan referred to in rule 18.1 include, but are not limited to:

(a) holding and maintaining details of the Option Holder's Options;

(b) transferring the Option Holder's Personal Data to the trustee of an employee benefit trust, the Company's registrars or brokers or any administrators of the Plan; and

(c) transferring the Option Holder's Personal Data to a bona fide prospective buyer of the Company or the Option Holder's employer company or business unit (or the prospective buyer's advisers), provided that the prospective buyer, and its advisers, irrevocably agree to use the Option Holder's Personal Data only in connection with the proposed transaction and in accordance with the data protection principles set out in the Data Protection Act 1998; and

(d) transferring the Option Holder's Personal Data under rule 18.3(b) or rule 18.3(c) to a person who is resident in a country or territory outside the European Economic Area that may not provide the same statutory protection for the information as countries within the European Economic Area.

19. GOVERNING LAW

The Plan and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with the law of England and Wales.

20. JURISDICTION

20.1 Each party irrevocably agrees that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with, the Plan or its subject matter or formation (including non-contractual disputes or claims).

20.2 Each party irrevocably consents to any process in any legal action or proceedings under rule 20.1 being served on it in accordance with the provisions hereof relating to service of notices. Nothing contained in the Plan shall affect the right to serve process in any other manner permitted by law.

Orchard Therapeutics Limited

Orchard Therapeutics Limited Employee Share Option Plan (the Plan)

Non-Employee Sub-Plan to the Orchard Therapeutics Limited Employee Share Option Plan (the Non-Employee Sub-Plan)

The Non-Employee Sub-Plan is adopted to permit the grant of options to individuals who are not employees or executive directors of the Company or any other Group Member.

In the event of any inconsistency between the rules of the Plan and the rules of the Non-Employee Sub-Plan, the rules of the Non-Employee Sub-Plan shall take precedence.

Unless otherwise stated in the individual Option Certificate, Grant Notice or Option Agreement, Options granted under the Non-Employee Sub-Plan are exercisable only from the earliest to occur of (a) the date of termination of the Eligible Person (other than for Summary Dismissal); (b) an event under Rule 12 of the Plan and (c) the fourth anniversary of the Grant Date.

1. DEFINITIONS

1.1 In this Non-Employee Sub-Plan, the words and expressions used in the Plan shall bear unless the context otherwise requires, the same meaning herein save to the extent the Rules in this Non-Employee Sub-Plan shall provide to the contrary.

1.2 In this Non-Employee Sub-Plan, the following words and expressions shall have the following meanings:

Eligible Person: means an individual who provides advisory or consultancy services to the Company or any Group Member either directly or through a company or other trading arrangement under a contract for the provision of services or otherwise and whether with the individual himself or with a company or other trading arrangement, or is a non-executive director of the Company or any Group Member; and

Relevant Company: the Group Member which is in relation to an Option Holder the company by which he holds office or to which he provides advisory or consultancy services.

1.3 This Non-Employee Sub-Plan is not an employees' share plan within the meaning of section 1166 of the Companies Act 2006.

2. APPLICATION OF PLAN

Save as modified in this Non-Employee Sub-Plan, all the provisions of the Plan shall be incorporated into this Non-Employee Sub-Plan as if fully set out herein so as to be part of this Non-Employee Sub-Plan.

3. ELIGIBLE PERSON ETC

3.1 Any references in the Plan to "**Employee**" shall be taken for the purposes of this Non-Employee Sub-Plan to be references to "**Eligible Person**" as defined in paragraph 1.2 of this Non-Employee Sub-Plan.

3.2 Any reference in the Plan to "Employer" shall be taken for the purposes of this Non-Employee Sub-Plan to be references to "**Relevant Company**" as defined in paragraph 1.2 of this Non-Employee Sub-Plan.

3.3 Rule 5.3 of the Plan shall be removed and replaced for the purposes of this Non- Employee Sub-Plan by the following:

"Subject to rule 5.4, an Option Holder may not exercise an Option at any time:

(a) *while disciplinary proceedings by any Group Member are underway against him; or*

(b) *while any Group Member is investigating his conduct and may as a result begin disciplinary proceedings; or*

(c) *while there is a breach of his contract for the provision of services or letter of appointment that is a potentially reason for the termination of his services or dismissed from office; or*

(d) *while he is in breach of a fiduciary duty owed to any Group Member; or*

(e) *after he has ceased to be an Eligible Person, if there was a breach of his contract for the provision of services or letter of appointment that (in the reasonable opinion of the Board) would have prevented the exercise of the Option had the Company been aware (or fully aware) of that breach, and of which the Company was not aware (or not fully aware) until after both:*

(i) *his ceasing to be an Eligible Person; and*

(ii) *the time (if any) when the Board decided to permit him to exercise his Option.*"

3.4 Rule 8 of the Plan shall be removed and replaced for the purposes of this Non- Employee Sub-Plan by the following.

"*8.* ***TERMINATION OF CONTRACT FOR SERVICES***

8.1 If an Option Holder dies, his personal representatives may exercise such proportion of his Option as the Board may specify (not being less than the Minimum Proportion measured at the date of death) during the period ending 12 months after his death.

8.2 An Option Holder who gives or receives notice of termination of his contract for services or letter of appointment or who ceases to be an Eligible Person for any reason other than Summary Dismissal may exercise such proportion of his Option as the Board may specify (not being less than the Minimum Proportion measured at the cessation date) during the period of 90 days after ceasing to be an Eligible Person and it shall lapse at the end of that period.

8.3 An Option Holder shall not be regarded as ceasing to be an Eligible Person until he is no longer providing services to or appointed a director of any Group Member."

3.5 Rule 9.2(e) of the Plan shall be removed and replaced for the purposes of this Non- Employee Sub-Plan by the following:

"9.2(e) if rule 8.2 applies the earlier of the date 90 days after the Option Holder ceases to be an Eligible Person or the date of the Summary Dismissal;

3.6 Rule 11 of the Plan shall be removed and replaced for the purposes of this Non- Employee Sub-Plan by the following:

"***11. RELATIONSHIP WITH CONTRACT FOR SERVICES***

11.1 The rights and obligations of any Option Holder under the terms of his contract for the provision of services or letter of appointment with any Group Member or former Group Member shall not be affected by being an Option Holder.

11.2 The value of any benefit realised under the Plan by Option Holders shall not be taken into account in determining any pension or similar entitlements.

11.3 Option Holders and Eligible Persons shall have no rights to compensation or damages on account of any loss in respect of Options where such loss arises (or is claimed to arise), in whole or in part, from:

(a) termination of his contract for the provisions of services with or his appointment to; or

(b) notice to terminate his contract for the provisions of services with or his appointment given by or to,

any Group Member or former Group Member. This exclusion of liability shall apply however termination of the contract for the provision of services or appointment, or the giving of notice, is caused, and however compensation or damages may be claimed.

11.4. Option Holders and Eligible Persons shall have no rights to compensation or damages from any Group Member or former Group Member on account of any loss in respect of Options where such loss arises (or is claimed to arise), in whole or in part, from:

(a) any company ceasing to be a Group Member; or

(b) the transfer of any business from a Group Member to any person which is not a Group Member.

This exclusion of liability shall apply however the change of status of the relevant Group Member, or the transfer of the relevant business, is caused, and however compensation or damages may be claimed.

11.5. An Eligible Person shall not have any right to receive Options, whether or not he has previously been granted any."

4. GOVERNING LAW

The Non-Employee Sub-Plan and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with the law of England and Wales.

5. JURISDICTION

5.1 Each party irrevocably agrees that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with, the Non-Employee Sub-Plan or its subject matter or formation (including non-contractual disputes or claims).

5.2 Each party irrevocably consents to any process in any legal action or proceedings under rule 5.1 above being served on it in accordance with the provisions hereof relating to service of notices. Nothing contained in the Non-Employee Sub- Plan shall affect the right to serve process in any other manner permitted by law.

Orchard Therapeutics Limited

Orchard Therapeutics Limited Employee Share Option Plan (the Plan)

US Sub-Plan to the Orchard Therapeutics Limited Employee Share Option Plan (the US Sub-Plan)

This US Sub-Plan together with the California supplement is adopted to permit the grant of options to an employee, director or consultants who are US residents or US taxpayers (each, a "**US Participant**").

In the event of any inconsistency between the rules of the Plan (and the Non-Employee Sub-Plan) and the rules of the US Sub-Plan, the rules of the US Sub-Plan shall take precedence.

Unless otherwise stated in the individual Option Certificate, Grant Notice or Option Agreement, Options granted under the US Sub-Plan are exercisable only from the earliest to occur of (a) the date of termination of Continuous Service (other than for Cause); (b) an event under Rule 12 of the Plan and (c) the fourth anniversary of the Grant Date.

1. DEFINITIONS

In this US Sub-Plan, the words and expressions used in the Plan (and the Non-Employee Sub-Plan) shall bear, unless the context otherwise requires, the same meaning herein save to the extent the Rules in this US Sub-Plan shall provide to the contrary.

In addition:

"**Continuous Service**" means that the Option Holder's service with the Company or any Group Member, whether as an Employee or Eligible Person, is not interrupted or terminated and the Option Holder remains an employee, director or Eligible Person. A change in the capacity in which the Option Holder renders service to the Company or a Group Member as an Employee or Eligible Person or a change in the entity for which the Option Holder renders such service, will not cause the Option Holder to cease to be an Employee or Eligible Person provided that there is no interruption or termination of the Option Holder's service with the Company or Group Member. To the extent permitted by law, the Board or the chief executive officer of the Company, in that party's sole discretion, may determine whether Continuous Service will be considered interrupted in the case of (i) any leave of absence approved by the Board or chief executive officer, including sick leave, military leave or any other personal leave, or (ii) transfers between the Company, a Group Member or their successors.

"**Cause**" will have the meaning ascribed to such term in any written agreement between the Option Holder and the Company or a Group Member defining such term and, in the absence of such agreement, such term means the occurrence of any of the following events: (i) the commission of any felony or any crime involving fraud, dishonesty or moral turpitude under the laws of the United States or any state thereof; (ii) the attempted commission of, or participation in, a fraud or act of dishonesty against the Company or any Group Member; (iii) the intentional, material violation of any contract or agreement between the Option Holder and the Company or any Group Member or of any statutory duty owed to the Company or any Group Member; (iv)the unauthorized use or disclosure of the Company's or any Group Member's confidential information or trade secrets; or (v) gross misconduct. The determination of Cause will be made by the Company, in its sole discretion.

2. APPLICATION OF PLAN

Save as modified in this US Sub-Plan, all the provisions of the Plan shall be incorporated into this US Sub-Plan as if fully set out herein so as to be part of this US Sub-Plan.

3. LIMIT

The number of Shares which may be subject to Options under this US Sub-Plan is 8,665,584 Shares (which number shall be the maximum number of Shares that may be granted as Options designated as Incentive Stock Options (as hereinafter defined)). No Option shall be granted under the US Sub-Plan unless there shall be sufficient Shares remaining available for issuance under the US Sub-Plan pursuant to this Section 3 or the Board shall have approved such an increase in the Shares available for issuance under the US Sub-Plan subject to Shareholder approval.

4. EFFECTIVE DATE AND TERM OF US SUB-PLAN

This US Sub-Plan shall become effective on the date on which it is adopted by the Board. No Option shall be granted under this US Sub-Plan after the completion of 10 years from the earlier of (i) the date on which this US Sub-Plan was adopted by the Board, or (ii) the date this US Sub-Plan was approved by the shareholders of the Company, but Options previously granted under this US Sub-Plan may extend beyond that date.

5. AMENDMENTS

The Board may amend, suspend or terminate this US Sub-Plan or any portion thereof at any time. No amendment, suspension or termination of the US Sub-Plan may materially adversely affect any Options granted previously to any US Participant without the consent of the US Participant. Continuance of this US Sub-Plan shall be subject to approval by the shareholders of the Company within twelve (12) months before or after the date the US Sub-Plan is adopted. Any Shares purchased under this US Sub-Plan before shareholder approval is obtained must be rescinded if shareholder approval is not obtained within twelve (12) months before or after the US Sub-Plan is adopted.

6. COMPLIANCE WITH CODE SECTION 409A

Unless otherwise set forth in an applicable Option Certificate, the terms applicable to Options granted under the Plan subject to this US Sub-Plan will be interpreted to the greatest extent possible in a manner that makes the Options exempt from Section 409A of the Internal Revenue Code of 1986, as amended, and any regulations promulgated thereunder (the "**Code**"), and, to the extent not so exempt, that brings the Options into compliance with Section 409A of the Code. Notwithstanding anything to the contrary in the Plan (and unless any Option agreement governing the Option specifically provides otherwise), if the Shares are publicly traded, and if an Option Holder of an Option that constitutes "deferred compensation" under Section 409A of the Code is a "specified employee" under Section 409A of the Code, no distribution or payment of any amount that is due because of a "separation from service" (as defined in Section 409A of the Code without regard to alternative definitions thereunder) will be issued or paid before the date that is six (6) months following the date of such Option Holder's "separation from service" or, if earlier, the date of the Option Holder's death, unless such distribution or payment can be made in a manner that complies with Section 409A of the Code, and any amounts so deferred will be paid in a lump sum on the day after such six (6) month period elapses, with the balance paid thereafter on the original schedule. The Company shall have no liability to an Option Holder, or any other party, if an Option that is intended to be exempt from, or compliant with, Section 409A of the Code is not so exempt or compliant or for any action taken by the Board.

7. NO RIGHT TO EMPLOYMENT OR OTHER STATUS

No person shall have any claim or right to be granted an Option under this US Sub-Plan, and the grant of an Option shall not be construed as giving an Option Holder the right to continued employment or any other relationship with any Group Member.

8. AMENDMENT OF OPTIONS

The Board may amend, modify or terminate any outstanding Option, including but not limited to, substituting therefor another Option of the same or different type, changing the date of exercise or realization, and converting an Incentive Stock Option to a Nonstatutory Stock Option, provided that the Option Holder's consent to such action shall be required unless the Board determine that the action, taking into account any related action, would not materially and adversely affect the Option Holder.

9. ELIGIBILITY LIMITATIONS FOR GRANTS TO ELIGIBLE PERSONS

An Eligible Person (as defined in the Non-Employee Sub-Plan) that is a US Participant is not eligible for the grant of an Option if, at the time of grant, either the offer or sale of the Company's securities to such Eligible Person is not exempt under Rule 701 of the Securities Act of 1933, as amended (the "**Securities Act**") because the Eligible Person is not a natural person, the services that the Eligible Person is providing to the Company or any Group Member are in connection with a capital raising transaction or directly or indirectly serve to promote or maintain a market for the Company's securities, or because of any other provision of Rule 701 of the Securities Act, unless the Company determines that such grant need not comply with the requirements of Rule 701 of the Securities Act and will satisfy another exemption under the Securities Act as well as comply with the securities laws of the US state of residence of the Eligible Person and all other applicable jurisdictions. Any Option granted to an Eligible Person that is a US Participant will be a Nonstatutory Stock Option (as hereinafter defined).

10. CONDITIONS ON DELIVERY OF SHARES

The Company will not be obligated to deliver any Shares pursuant to this US Sub-Plan or to remove restrictions from Shares previously delivered under this US Sub-Plan until:

10.1. all conditions of the Option have been met or removed to the satisfaction of the Company;

10.2. in the opinion of the Company's counsel, all other legal matters in connection with the issue, allotment and delivery of such shares have been satisfied, including any applicable securities laws and any applicable stock exchange or stock market rules and regulations; and

10.3. the Option Holder has executed and delivered to the Company such representations or agreements as the Company may consider appropriate to satisfy the requirements of any applicable laws, rules or regulations.

11. GRANT OF OPTIONS

11.1. An Option which is not intended to be an Incentive Stock Option (as hereinafter defined) shall be designated a "Nonstatutory Stock Option". Notwithstanding anything to the contrary in the Plan, the Grant Date of an Option for the purposes of the US Sub-Plan shall be the date on which the Board resolves to grant an Option.

11.2. An Option shall have a term no longer than ten (10) years from the date it was granted or such shorter period as determined by the Board. If an Incentive Stock Option is granted to a person who owns more than 10% of the total combined voting power of all classes of outstanding stock of the Company or any of its affiliates, the Option shall have a term no longer than five (5) years from the date it was granted.

11.3. The Exercise Price of (a) an Option intended to be an Incentive Stock Option and (b) any Non-statutory Stock Option granted to a US Participant shall be not less than 100% of the fair market value of a Share on the date on which the Option is granted (which shall be determined by the Board in compliance with Section 409A of the Code and shall not be less than the nominal value of a Share) ("**Fair Market Value**") unless, in the case of (b) such Option is structured to comply with Section 409A of the Code.

11.4. An Option that the Board intends to be an "incentive stock option" as defined in Section 422 of the Code (an "**Incentive Stock Option**") shall only be granted to Employees who are also employees of the Company, any of the Company's present or future parent or subsidiary corporations as defined in Treasury Regulation Section 1.424-1(f), and any other entities the employees of which are eligible to receive Incentive Stock Options under the Code, and shall be subject to and shall be construed consistently with the requirements of Section 422 of the Code. The Board or corporate action approving the grant of an Option intended to be an Incentive Stock Option must specify that the Option is intended to be an Incentive Stock Option. If an Option is not specifically designated as an Incentive Stock Option, or if an Option is designated as an Incentive Stock Option but some portion or all of the Option fails to qualify as an Incentive Stock Option under the applicable rules, then the Option (or portion thereof) will be a Nonstatutory Stock Option. The Company shall have no liability to an Option Holder, or any other party, if an Option (or any part thereof) that is intended to be an Incentive Stock Option is not an Incentive Stock Option or for any action taken by the Board to amend, modify or terminate the rules of the Plan, this US Sub-Plan or any Option, including without limitation the conversion of an Incentive Stock Option to a Nonstatutory Stock Option.

11.5. As provided by Section 422(b)(5) of the Code, an Incentive Stock Option will not be transferable except by will or by the laws of descent and distribution, and will be exercisable during the lifetime of the US Participant only by the US Participant. If the Board elects to allow the transfer of an Option by a US Participant that is designated as an Incentive Stock Option, such transferred Option will automatically become a Nonstatutory Stock Option. As provided by Section 422(c)(5) of the Code, a person who owns more than 10% of the total combined voting power of all classes of outstanding stock of the Company or any Group Member will not be eligible for the grant of an Incentive Stock Option *unless* (i) the exercise price is at least 110% of the Fair Market Value of a Share on the date of grant and (ii) such Incentive Stock Option by its terms is not exercisable after the expiration of five (5) years from the date of grant. The attribution rules of Section 424(d) of the Code will be applied in determining stock ownership. As provided by Section 422(d) of the Code and applicable regulations thereunder, to the extent that the aggregate Fair Market Value (determined at the time of grant) of Shares with respect to which Incentive Stock Options are exercisable for the first time by any US Participant during any calendar year (under all plans of the Company and any Group Member) exceeds US$100,000 (or such other limit established in the Code) or otherwise does not comply with the rules governing Incentive Stock Options, the Options or portions thereof that exceed such limit (according to the order in which they were granted) or otherwise do not comply with such rules will be treated as Nonstatutory Stock Options. To obtain the US federal income tax advantages associated with an Incentive Stock Option, the US Internal Revenue Code requires that at all times beginning on the date of grant and ending on the day three (3) months before the date of exercise of the Option, the Option Holder must be an Employee of the Company or a Group Member (except in the event of the Option Holder's death or Disability (as defined below), in which case longer periods may apply).

11.6. Notwithstanding Rules 9.1 and 9.2(a) of the Plan, where an Option Holder ceases to be an Employee or Eligible Person by reason of his death his Option will be capable of transfer in accordance with the Option Holder's will, or the laws of decent and distribution. Subject to the approval of the Board or a duly authorized officer of the Company, an Option Holder may, by delivering written notice to the Company, in a form approved by the Company, designate a third party who, on the death of the Option Holder, will thereafter be entitled to exercise the Option and receive the Shares or other consideration resulting from such exercise. In the absence of such a designation, upon the death of the Option Holder, the executor or administrator of the

Option Holder's estate will be entitled to exercise the Option and receive the Shares or other consideration resulting from such exercise. However, the Company may prohibit designation of a beneficiary at any time, including due to any conclusion by the Company that such designation would be inconsistent with the provisions of applicable laws. In addition, notwithstanding Rules 9.1 and 9.2(a) of the Plan, subject to approval of the Board or a duly authorized officer of the Company, an Option may be transferred by an Option Holder pursuant to the terms of a domestic relations order, official marital settlement agreement or other divorce or separation instrument as permitted by Treasury Regulations Section 1.421-1(b)(2); provided that if an Option is an Incentive Stock Option, such Option will be deemed to be a Nonstatutory Stock Option as a result of such transfer.

11.7. Shares purchased upon the exercise of an Option granted under this US Sub-Plan shall be paid for as follows:

(a) in cash or by check, payable to the order of the Company;

(b) except as may otherwise be provided in the applicable Option Certificate and to the extent the Shares are publicly traded, by:

(i) delivery of an irrevocable and unconditional undertaking by a creditworthy broker to deliver promptly to the Company sufficient funds to pay the exercise price and any required tax withholding; or

(ii) delivery by the Option Holder to the Company of a copy of irrevocable and unconditional instructions to a creditworthy broker to deliver promptly to the Company cash or a check sufficient to pay the exercise price and any required tax withholding.

(c) As a condition to the exercise of an Option, the Option Holder shall make such arrangements as the Company may require for the satisfaction of any U.S. federal, state, local or foreign withholding tax obligations that may arise in connection with such exercise. The Option Holder shall also make such arrangements as the Company may require for the satisfaction of any federal, state, local or foreign withholding tax obligations that may arise in connection with the disposition of Shares acquired by exercising an Option.

12. EXERCISE RESTRICTION FOR NON-EXEMPT EMPLOYEES

If an Option Holder is an Employee who is eligible for overtime compensation under the US Fair Labor Standards Act of 1938, as amended (that is, the Option Holder is designated as a "non-exempt employee"), then notwithstanding the vesting schedule contained in the Option Certificate, the Option Holder may not exercise his or her Option until the Option Holder has completed at least six (6) months of Continuous Service measured from the Grant Date, even if the Option Holder has already been an Employee for more than six (6) months. Consistent with the provisions of the U.S. Worker Economic Opportunity Act, the Option Holder may exercise his or her Option as to any vested portion prior to such six (6) month anniversary in the case of (i) the Option Holder's death or the Option Holder becoming disabled (within the meaning of Section 22(e)(3) of the Code), (ii) an Offeror obtains Control of the Company, or (iii) the termination of the Option Holder's Continuous Service on his or her "retirement" (as defined in the Company's benefit plans).

13. EXERCISE OF OPTIONS IN SPECIAL CIRCUMSTANCES

If an Option Holder dies or becomes disabled (within the meaning of Section 22(e)(3) of the Code) ("**Disability**") before the tenth anniversary of the Grant Date, the provisions of Rules 8.1, 8.2, 9.2(d) and 9.2(e) of the Plan shall not apply for the purposes of this US Sub-Plan. Instead, in such circumstances, Options may be exercised for a period of 18 months following the date of death or 12 months following the date of Disability, but in no event later than the tenth anniversary of the relevant Grant Date.

14. DISQUALIFYING DISPOSITION

If the Option Holder disposes of Shares acquired upon exercise of an Incentive Stock Option within two years from the Grant Date or one year after such Shares were acquired pursuant to exercise of such Option, the Option Holder shall notify the Company in writing of such disposition.

15. VARIATION OF SHARE CAPITAL

Notwithstanding Rule 14 of the Plan in the event of any variation of the share capital of the Company: (i) the number of Shares subject to an Option; (ii) the Exercise Price; and (iii) the limit on Options set forth in Section 3 hereof must be adjusted proportionately in a manner that complies with Sections 409A and 424 of the Code; PROVIDED THAT the Exercise Price may not be reduced below the nominal value of a Plan Share except where the Board puts in place arrangements to pay up the nominal value at the date of issue of the Shares (or the difference between the adjusted Exercise Price and the nominal value as the case may be).

16. NO OBLIGATION TO NOTIFY OR MINIMIZE TAXES

The Company will have no duty or obligation to an Option Holder to advise such holder as to the time or manner of exercising the Option. Furthermore, the Company will have no duty or obligation to warn or otherwise advise such holder of a pending termination or expiration of an Option or a possible period in which the Option may not be exercised. The Company has no duty or obligation to minimize the tax consequences of an Option to the Option Holder.

17. GOVERNING LAW

The US Sub-Plan and any dispute or claim arising out of or in connection with it or its subject matter or formation (including non-contractual disputes or claims) shall be governed by and construed in accordance with the law of England and Wales.

18. JURISDICTION

18.1 Each party irrevocably agrees that the courts of England and Wales shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with, the US Sub-Plan or its subject matter or formation (including non-contractual disputes or claims).

18.2 Each party irrevocably consents to any process in any legal action or proceedings under rule 18.1 above being served on it in accordance with the provisions hereof relating to service of notices. Nothing contained in the US Sub-Plan shall affect the right to serve process in any other manner permitted by law.

CALIFORNIA SUPPLEMENT

The Board has adopted this supplement for purposes of satisfying the requirements of Section 25102(o) of the California Law:

Any Options granted under the US Sub-Plan to the Plan to an Option Holder who is a resident of the State of California on the date of grant (a "California Option Holder") shall be subject to the following additional limitations, terms and conditions:

1. ADDITIONAL LIMITATIONS ON OPTIONS.

Minimum Exercise Period Following Termination. Unless a California Option Holder's employment is terminated for cause (as defined by applicable law, the terms of any contract of employment between the Company and such Option Holder, or in the instrument evidencing the grant of such Option Holder's Option), in the event of termination of employment of such Option Holder, such Option Holder shall have the right to exercise an Option, to the extent that he or she was otherwise entitled to exercise such Option on the date employment terminated, until the earlier of: (i) at least six months from the date of termination, if termination was caused by such Option Holder's death or Disability; (ii) at least 30 days from the date of termination, if termination was caused other than by such Option Holder's death or Disability; and (iii) the Option expiration date.

2. ADDITIONAL LIMITATIONS ON TIMING OF AWARDS.

No Option granted to a California Option Holder shall become exercisable, vested or realizable, as applicable to such Option, unless the US Sub-Plan has been approved by the holders of a majority of the Company's outstanding voting securities by the later of (i) within 12 months before or after the date the US Sub-Plan was adopted by the Board or (ii) prior to or within 12 months of the granting of any Option to a California Option Holder.

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

TABLE OF CONTENTS

1. INTERPRETATION 3
2. NOVATION 4
3. WARRANTIES 6
4. CONFIRMATION OF TERMS 6
5. LIMITATION PERIODS 7
6. GOVERNING LAW 7
7. JURISDICTION 7

Schedule 1 11

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
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

Pre-clinical Agreements

[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

Clinical Agreements

[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

[***]	[***]	[***]
[***]	[***]	[***]
[***]	[***]	[***]

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

TABLE OF CONTENTS

1	DEFINITIONS	4
2	RESEARCH AND DEVELOPMENT UNDER THE ALLIANCE	22
3	MANAGEMENT OF THE COLLABORATION	36
4	GRANT OF RIGHTS	45
5	POST-EXERCISE and POST-LICENSE ACTIVITIES	58
6	MILESTONES AND ROYALTIES; PAYMENTS	61
7	EXCLUSIVITY	70
8	INTELLECTUAL PROPERTY	72
9	CONFIDENTIALITY	84
10	REPRESENTATIONS AND WARRANTIES	90
11	INDEMNIFICATION; INSURANCE	94
12	TERM AND TERMINATION	98
13	MISCELLANEOUS	109

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) [***] 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 ***

14 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."

15 [***]—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).

16 Amendment of Article 4 of the Collaboration Agreement.

16.1 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."

17 Amendment of the Development Plan for the Beta-Thal Program Clinical Studies.

17.1 **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.

17.2 The Development Plan for the Beta-Thal Program shall be amended to:

(a) 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

(b) 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.

17.3 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.

17.4 **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).

17.5 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 [***].

17.6 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.

17.7 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).

18 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."

19 Milestones and Royalties; Payments.

19.1 Amendment of Clause 6.1 (Upfront Payment) of the Collaboration Agreement.

(a) 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."

19.2 *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	
[***]	[***]
[***]	[***]

**[***]
***[***]
****[***]

19.3 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.

20 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.

21 Anti-Bribery, Anti-Corruption.

21.1 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.

21.2 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.

21.3 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.

22 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:

22.1 *Side Letter No. 1*: [***];

22.2 *Side Letter of* [***].

22.3 *Side Letter No. 2*: [***];

22.4 *Side Letter No. 3*: [***];

22.5 *Side Letter No. 4*: [***];

22.6 *Side Letter No. 5*: [***];

22.7 *Side Letter No. 6*: [***]; and

22.8 *Side Letter No. 7*: [***].

22.9 Side letter No. 8: [***].

22.10 *Side letter No. 9*: [***].

23 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."

24 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

25 **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").**

26 **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.

27 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:

27.1 *Side Letter No. 1*: [***];

27.2 *Side Letter of [***]*.

27.3 *Side Letter No. 2*: [***];

27.4 *Side Letter No. 3*: [***];

27.5 *Side Letter No. 4*: [***];

27.6 *Side Letter No. 5*: [***];

27.7 *Side Letter No. 6*: [***]; and

27.8 *Side Letter No. 7*: [***].

27.9 *Side letter No. 8*: [***].

27.10 *Side letter No. 9*: [***].

27.11 *Side letter No. 10*: [***].

28 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.

--*-*-*-*-*-*-*-*-*

[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.

--*-*-*-*-*-*-*-*-*-*-

[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.**

--*-*-*-*-*-*-*-*-*

[*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

5 **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 [***].**

	Programs M £						
Milestone Events	**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:

- [***]
- [***]

6 **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.**

7 **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.**

--*-*-*-*-*-*-*-*

[*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 [***].

1.1 *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.

1.2 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-Thai 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 <u>Payment for Additional Beta Thal Lentiviral Vector Batches. As of this Amendment No 6 Effective Date:</u>

1.1 Telethon-OSR and GSK agreed to have a [***] Beta Thal lentiviral vector batch produced at a rate of [***] per batch;

1.2 GSK has already entirely reimbursed the above mentioned amount in accordance with Section 2 of Amendment No. 2;

1.3 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.

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: [***]

DATED JANUARY 19, 2018

NEW CONNECT INVESTMENTS LIMITED

AND

ORCHARD THERAPEUTICS LIMITED

LEASE OF 2nd and 3rd FLOOR, 108 CANNON STREET, LONDON

Lewis Silkin LLP
5 Chancery Lane
Clifford's Inn
London EC4A 1BL

(Ref: EMH8296/112671.14)

CONTENTS

1	DEFINITIONS AND INTERPRETATION	3
2	DEMISE TERM RENT AND RENT PAYMENT DATES	9
3	TENANT'S COVENANTS REFERRING TO SCHEDULE 3	10
4	LANDLORD'S COVENANTS REFERRING TO SCHEDULE 4	10
5	PROVISOS REFERRING TO SCHEDULE 5	10
6	INCORPORATION OF SCHEDULES 6, 7, 8 AND 9	10
7	IMPLIED RIGHTS OF ENFORCEMENT BY THIRD PARTIES EXCLUDED	10
8	TENANT'S OPTION TO DETERMINE	10
	SCHEDULE 1	12
	SCHEDULE 2	16
	SCHEDULE 3	17
	SCHEDULE 4	30
	SCHEDULE 5	31
	SCHEDULE 6	35
	SCHEDULE 7	40
	SCHEDULE 8	49
	SCHEDULE 9	50

LAND REGISTRY PRESCRIBED CLAUSES

LR1 Date of lease	19 January 2018
LR2 Title number(s)	**LR2.1 Landlord's title number(s)** LN38304 **LR2.2 Other title numbers** None
LR3 Parties to this lease	**Landlord** **New Connect Investments Limited**, a company incorporated in the British Virgin Islands with company number 1920596 and whose registered office is at PO Box 957, Offshore Incorporations Centre, Road Town, Tortola, British Virgin Islands whose address for service in England and Wales is care of **Nan Fung UK Properties Limited** (company registration number 09543279) whose registered office is at 3rd Floor, 11-12 St James's Square, London, United Kingdom SW1Y 4LB (whose correspondence address is at The Pavilion, 96 Kensington High Street, London W8 4SG) **Tenant** **ORCHARD THERAPEUTICS LIMITED** a company incorporated in England and Wales (registered number 09759506) whose registered office is at Birchin Court, 20 Birchin Lane, London, England EC3V 9DU Other parties None
LR4 Property	In the case of a conflict between this Clause and the remainder of this Lease then for the purposes of registration this Clause shall prevail. The Premises as defined in Schedule 1
LR5 Prescribed statements etc	**LR5.1** Not applicable **LR5.2** Not applicable
LR6 Term for which the Property is leased	The **Term** is as follows: Five years from and including 8 January 2018 and expiring on 7 January 2023
LR7 Premium	None
LR8 Prohibitions or restrictions on disposing of this lease	**The lease contains a provision that prohibits or restricts dispositions**

LR9 Rights of acquisition etc	**LR9.1 Tenant's contractual rights to renew this lease to acquire the reversion or another lease of the Property or to acquire an interest in other land** None **LR9.2 Tenant's covenant to (or offer to) surrender this lease** None **LR9.3 Landlord's contractual rights to acquire this lease** None
LR10 Restrictive covenants given in this lease by the Landlord in respect of land other than the Property	None
LR11 Easements	**LR11.1 Easements granted by this lease for the benefit of the Property The rights and matters set out in Schedule 1 Part 2 LR11.2 Easements granted or reserved by this lease over the Property for the benefit of other property The rights and matter set out in Schedule 1 Part 3**
LR12 Estate rentcharge burdening the Property	None
LR13 Application for standard form of restriction	None
LR14 Declaration of trust where there is more than one person comprising the Tenant	Not applicable

OPERATIVE PROVISIONS

1 DEFINITIONS AND INTERPRETATION

1.1 In this Lease:

"1954 Act"

means the Landlord and Tenant Act 1954;

"Authorised Guarantee Agreement"

means an agreement as defined in s.16 of the Landlord and Tenant (Covenants) Act 1995 in a form to be determined by the Landlord acting reasonably;

"Base Rate Interest"

means Interest at an annual rate equal to the base rate of HSBC Bank plc (or if that rate ceases to be published such other comparable rate of interest as the Landlord shall reasonably specify) from time to time;

"Break Date"

means 8 January 2022;

"Building"

means the building known as 108 and 108a Cannon Street and 3 and 4 Laurence Pountney Lane registered at the Land Registry under title number LN38304 including landlord's fixtures and fittings and any areas owned by the Landlord and used and enjoyed with it and any extensions or additions to it;

"Category A Specification"

means the specification annexed to this Lease in Schedule 9;

"CDM Regulations"

means the Construction (Design and Management) Regulations 2015 as amended supplemented or replaced from time to time;

"Commercial Rent Arrears Recovery"

means the procedure by which a landlord can recover rent arrears due under a commercial lease from a tenant pursuant to the Tribunals, Courts and Enforcement Act 2007 (as amended, varied, supplemented or re-enacted from time to time);

"Common Media"

means Conducting Media serving the Building but not exclusively serving any Lettable Area;

"Common Parts"

means all parts of the Building available for general use from time to time in common with the Landlord and the lawful occupiers of the Building;

"Conducting Media"

means pipes, wires, cables, sewers, drains, watercourses, trunking, ducts, flues, gutters, gullies, channels, conduits, and other media but not including any service risers or any other airspace through which the media run;

"CRC Participant"

means the Landlord, any participant from time to time responsible for compliance with the Energy Scheme in respect of the Building and any Group Undertaking of the Landlord or that participant where "Participant" and "Group Undertaking" have the meanings given to them in the CRC Energy Efficiency Scheme Order 2013;

“Dispute”

means any dispute or difference which may arise between the Landlord and the Tenant concerning:

(a) the amount or duration of the rent to be abated pursuant to paragraph 3.1 or 5.2(a) of Schedule 6; and

(b) any dispute arising as a result of a failure to resolve any issue under paragraph 3.6 of Schedule 7, Part 1;

“Dispute Resolution Procedure”

means the procedure for the resolution of any Dispute as set out in paragraph 15 of Schedule 5;

“Electronic Communications Apparatus”

means “electronic communications apparatus” as defined in schedule 2 to the Telecommunications Act 1984 as amended by the Communications Act 2003;

“Encumbrances”

means the matters contained or referred to in the documents identified in Schedule 2;

“Energy Costs”

means the aggregate of:

(a) the anticipated or actual costs and charges incurred by or on behalf of any CRC Participant in purchasing carbon allowances in relation to the Energy Scheme; and

(b) the management costs relating to the implementation of, participation in and operation of the Energy Scheme incurred by or on behalf of any CRC Participant;

“Energy Scheme”

means the Carbon Reduction Commitment Energy Efficiency Scheme administered in accordance with the CRC Energy Efficiency Scheme Order 2013 or any later order or any similar scheme amending or replacing it;

“Environment”

means all or any of the following media, namely air (including air within building or other natural or manmade structures whether above or below ground), water (including groundwater and water in pipe and sewerage systems) and land;

“Environmental Rating”

means any rating generated from time to time by the Environmental Rating System in respect of the Premises and/or the Building;

“Environmental Rating System”

means any rating system for the Premises/Building mandated by legislation for the purposes of measuring the environmental efficiency and/or performance of the Premises/Building including but not limited to the systems used for EPCs and BREEAM;

“EPC”

means an Energy Performance Certificate and Recommendation Report as defined in the Energy Performance of Buildings (England and Wales) Regulations 2012 as amended or updated from time to time;

“Excluded Plant”

means the plant and machinery and Conducting Media comprised in the central heating and hot water system air-conditioning and ventilation system serving:

(a) the Premises in common with other parts of the Building; and/or

(b) exclusively serving the Premises but connected to a system serving other parts of the Building including any items installed by the Tenant or anyone claiming title to the Premises through or under the Tenant;

"Existing EPC"

means a copy of the EPC for the Building reference no 9851-3078-03620400-4105;

"Expert"

means a chartered surveyor having not less than ten years' experience;

"Group Company"

means any company which is a member of the same group of companies as the Landlord or the Tenant (as the case may be) within the meaning of section 42(1) of the 1954 Act;

"Guarantor"

means any person who from time to time provides a guarantee and indemnity under the terms of this Lease excluding a guarantor under an Authorised Guarantee Agreement;

"Hazardous Materials"

means any substance whether in solid, liquid or gaseous form, which is capable of causing harm to human health or to the Environment whether on its own or in combination with any other substance;

"Higher Rate Interest"

means four per cent above Base Rate Interest;

"Insolvency Event"

means:

(a) in relation to a company

(i) the taking of any step in connection with any voluntary arrangement or other compromise, scheme or arrangement for the benefit of any creditors of the company;

(ii) the making of an administration order in relation to the company;

(iii) the appointment of an administrator in relation to the company;

(iv) the appointment of a receiver or an administrative receiver in relation to any property or income of the company;

(v) the making of a winding up order in respect of the company;

(vi) a resolution passed to voluntarily wind up the company (other than a resolution to wind up the company for the purpose of amalgamation or reconstruction of a solvent company);

(vii) the striking off of the company from the register of companies or the company otherwise ceasing to exist,

and these provisions shall apply mutatis mutandis in relation to a Partnership or Limited Partnership or Limited Liability Partnership (as defined in the Partnership Act 1890, the Limited Partnerships Act 1907 and the Limited Liability Partnerships Act 2000 respectively) except where the context requires otherwise and where relevant with the same modifications as referred to in the Insolvent Partnerships Order 1994 and the Limited Liability Partnerships Regulations 2001;

(b) in relation to an individual:

(i) the taking of any step in connection with any voluntary arrangement or other compromise, scheme or arrangement for the benefit of any creditors of the individual;

(ii) the making of a bankruptcy order against the individual;

(iii) the appointment of a trustee in bankruptcy in relation to the individual;

(c) where a person is incorporated or resident in a jurisdiction outside England and Wales, any event or circumstance that occurs which under the laws of that jurisdiction has an analogous or equivalent effect to any of the events in paragraphs (a) and (b) of this definition;

"Insured Risks"

means fire lightning explosion aircraft and articles dropped from them riot civil commotion malicious damage storm tempest flood earthquake bursting or overflowing of water tanks apparatus and pipes impact by any vehicle subsidence landslip ground heave terrorism and such other risks as the Landlord may reasonably consider necessary to insure, subject in all cases to any excesses, limitations and exclusions imposed by the insurers;

"Interest"

means interest calculated on a day-to-day basis (as well before as after judgment);

"Landlord"

means the party named as such in Clause LR3 and includes the reversioner for the time being immediately expectant on the Term;

"Landlord's Costs"

has the meaning given to it in Schedule 7, Part 1 paragraph 1.3;

"Landlord's Regulations"

means the reasonable regulations made by the Landlord from time to time and notified to the Tenant having regard to good estate management and the safety, precaution, maintenance, management and general amenity of the Building (including the reasonable regulations relating to the Roof Garden Terrace, the bike racks, lockers and Plant Area) save that in the event of any conflict between such regulations and the terms of this Lease, the terms of this Lease will prevail;

"Landlord's Surveyor"

means a surveyor or member of a firm of surveyors who shall be a member of the Royal Institution of Chartered Surveyors or suitably experienced and such surveyor may be a person employed by the Landlord or a company which is a Group Company;

"Lease"

means this Lease and includes:

(a) a licence or consent granted pursuant to;

(b) any variation of; and

(c) any deed or instrument made supplemental to this Lease;

"Lettable Areas"

means the area within the Building which is designated for and capable of exclusive beneficial occupation;

"Main Structure"

means the exterior and main structure of the Building including the foundations roofs windows load-bearing walls load-bearing columns ceilings and floors (but excluding any raised floors suspended ceilings all internal cladding plasterwork and decoration (save where internal to any Common Parts) and all floor screeding and finishes);

“Management Premises”

means all administrative security and control offices and centres and stores (if any) maintained by the Landlord for managing the Building and providing the Services and any accommodation for a caretaker housekeeper porter or facilities manager employed for purposes connected with the Building;

“Net Internal Area”

means net internal floor area measured in accordance with Definition 3 of the RICS Code of Measuring Practice (6th edition November 2007);

“Outgoings”

means all existing and future rates, taxes, charges, assessments, impositions, levies, contributions and outgoings at any time payable, charged or assessed on property or the owner or occupier of property in relation to the Building or the Premises or the owner or occupiers of them whether on a one-off, periodic or irregular basis and whether or not in the nature of capital or income payments but excluding any income or corporation tax imposed on the Landlord in respect of the grant of this Lease, the receipt of rents reserved by this Lease or any dealing or disposition by the Landlord of its interest in the Premises;

“Permitted Part”

means a part of the Premises consisting of any whole floor of the Premises;

“Permitted Use”

means use as high class offices within Class B1(a) of the Schedule to the Town and Country Planning (Use Classes) Order 1987 as in force at the date of this deed;

“Planning Acts”

means the Town and Country Planning Act 1990 and any other statutes, regulations and orders relating to town and country planning in force from time to time;

“Plans”

means any of the plans in this Lease;

“Plant Area”

means an area on the roof of the Building designated from time to time by the Landlord;

“Premises”

means the premises described in Schedule 1 Part 1;

“Reception Hours”

the hours between 8:00 am and 5:00 pm on Mondays to Fridays other than on public holidays provided that this will not limit the Tenant access to the Building and/or the Premises and the Tenant will have access 24 hours a day all year;

“Rent”

means the sums payable by the Tenant to the Landlord in accordance with clause 2;

“Rent Days”

means 25 March, 24 June, 29 September and 25 December in each year and the relevant Rent Day shall be construed accordingly;

“Rent Commencement Date”

means the Term Commencement Date;

“Roof Garden Terrace”

means that part of the eighth floor of the Building known as the roof terrace;

“Service Charge”

has the meaning given to it in Schedule 7, Part 1 paragraph 1.2;

"Services"

has the meaning given to it in Schedule 7, Part 1 paragraph 1.4;

"Tenant"

means the party named as such in Clause LR3 and includes the successors in title and assigns of the Tenant;

"Term"

means the term as set out in Clause LR6;

"Term Commencement Date"

means the first day of the Term;

"Trigger Event"

means any of the following:

(a) the disclaimer of this Lease by the Crown or by a liquidator or trustee in bankruptcy of the Tenant;

(b) the Tenant is struck off the register of companies or otherwise ceases to exist;

(c) the forfeiture of this Lease by the Landlord;

((a), (b) and (c) together being "**Termination Trigger Events**");

(d) the appointment of an administrator in respect of the Tenant;

(e) the proposal by the Tenant or any of its creditors for the Tenant to enter into any voluntary arrangement, scheme of arrangement or other arrangement with its creditors;

((d) and (e) together being "**Other Trigger Events**");

"Uninsured Risk"

means an Insured Risk against which insurance is not or ceases to be obtainable for such risks on normal commercial terms in the London insurance market at reasonable commercial rates generally available in the London insurance market for a property of this type size and location or excluded from being so by reason of withdrawal of cover by the insurer and which is not otherwise available to be insured on the London insurance market;

"VAT"

means value added tax and any other tax of a similar nature; and

"Wireless Data Services"

means the provision of wireless data, voice or video connectivity or wireless services permitting or offering access to the internet or any wireless network, mobile network or telecommunications system that involves a wireless or mobile device.

1.2 Where two or more persons are included in any expression the liability under any covenant or other obligation on their part shall be joint and several.

1.3 Any words or expressions importing the singular number include the plural number and vice versa and words importing gender include any other gender.

1.4 Unless otherwise specified any reference to an act of parliament includes a reference to that act as amended or replaced whether before or after the date of this Lease and to subordinate legislation or bylaws or regulations made under it and any general reference to statute or legislation includes subordinate legislation bylaws and regulations.

1.5 **"liability"** includes (where the context allows) claims demands proceedings damages losses costs and expenses.

1.6 Interest payable under this Lease is payable from and including the due date (which where appropriate will be the date of expenditure) until but excluding the date of payment.

1.7 Any reference to the end of the Term means the end or earlier termination of this Lease for whatever reason.

1.8 Where the Tenant is placed under a restriction by this Lease it includes an obligation not to permit or allow the restriction to be infringed by any person under the Tenant's control.

1.9 Reference to consent or approval not being unreasonably withheld also means it must not be unreasonably delayed.

1.10 Any consent or approval (where necessary) must be obtained before the act or event to which it applies is carried out or done and will be effective only if in the reasonable form the party giving it properly requires.

1.11 The Landlord's rights to enter under this Lease are exercisable also by its employees agents and workpeople and any others authorised by it.

1.12 The Tenant's rights to enter under this Lease are exercisable also by its employees agents and workpeople and any others authorised by it.

1.13 References to "sustainable" and "sustainability" shall:

(a) include the sourcing specification performance recycling and suitability for purpose of any materials processes or methodology; and

(b) the question of whether something is sustainable is to be judged at the time the issue arises and not at the date of this Lease.

1.14 Reference to **"adjoining premises"** means any land or buildings adjoining or nearby the Premises and the Building, whether or not owned by the Landlord.

1.15 **"includes", "including"** and similar words are used without limitation or qualification to the subject matter of the relevant provision.

1.16 If any provision is held to be illegal, invalid or unenforceable, the legality, validity and enforceability of the remainder of this Lease will be unaffected.

2 DEMISE TERM RENT AND RENT PAYMENT DATES

The Landlord lets the Premises with full title guarantee to the Tenant:

(a) with the rights set out in Schedule 1 Part 2;

(b) except and reserved to the Landlord the rights set out in Schedule 1 Part 3;

(c) for the Term;

(d) subject to the Encumbrances,

the Tenant paying during the Term:

(a) the yearly rent of £308,000 from the Rent Commencement Date until the expiry of twelve months and 34 days from the Rent Commencement Date, and £616,000 thereafter (being £306,310.50 in respect of the third floor and £309,689.50 in respect of the second floor per annum) by equal quarterly payments in advance on the Rent Days, the first payment to be calculated from the Rent Commencement Date to the day before the next quarter day (both dates inclusive) and to be made on the Rent Commencement Date PROVIDED THAT if this Lease is not determined in accordance with clause 8 the yearly rent from the day after the Break Date until the expiry of six months from the day after the Break Date will be £308,000 per annum;

(b) as additional rent the Service Charge the first payment being in respect of the period from and including the Term Commencement Date;

(c) within 10 working days of written demand as additional rent the sums specified in Schedule 6 the first payment to be made in respect of the period from and including the Term Commencement Date;

(d) as additional rent (and subject to receipt of a valid VAT invoice) any VAT which may be properly chargeable in respect of any rent payable under this Lease; and

(e) as additional rent any Interest and other sums payable under this Lease as rent under and at the times set out in this Lease.

3 TENANT'S COVENANTS REFERRING TO SCHEDULE 3

The Tenant covenants with the Landlord to observe and perform the covenants and stipulations in Schedule 3.

4 LANDLORD'S COVENANTS REFERRING TO SCHEDULE 4

The Landlord covenants with the Tenant to observe and perform the covenants and stipulations in Schedule 4.

5 PROVISOS REFERRING TO SCHEDULE 5

It is agreed and declared as stated in Schedule 5.

6 INCORPORATION OF SCHEDULES 6, 7, 8 AND 9

The provisions in Schedule 6, Schedule 7, Schedule 8 and Schedule 9 are incorporated.

7 IMPLIED RIGHTS OF ENFORCEMENT BY THIRD PARTIES EXCLUDED

7.1 Unless the right of enforcement is expressly granted it is not intended that a third party should have the right to enforce a provision of this Lease under the Contracts (Rights of Third Parties) Act 1999.

7.2 The parties may terminate or vary this Lease without the consent of a third party to whom an express right to enforce any of its terms has been provided.

8 TENANT'S OPTION TO DETERMINE

8.1 The Tenant can determine this Lease on the Break Date by giving to the Landlord not less than nine months' prior written notice and provided that the Tenant complies with the conditions set out in clause 8.2 below (the "**Break Conditions**").

8.2 The Break Conditions are that the Tenant shall:

(a) up until the Break Date have paid the yearly rent and Service Charge reserved by this Lease for the period up to and including the Break Date provided that such Service Charge has been demanded in writing at least 14 days prior to the Break Date;

(b) give up vacant possession of the Premises on the Break Date; and

(c) not have granted any sublease, licence to occupy or tenancy at will or any other occupation interests whatsoever in relation to the Premises or any part thereof which shall continue to subsist after the Break Date,

but the Tenant shall not be in breach of this clause 8.2 if on the Break Date there remain any Tenant fixtures, fittings or chattels of an inconsequential nature provided that the Landlord shall have the right to remove the same immediately on determination of the Lease at the sole cost of the Tenant.

8.3 On the expiry of such notice the Term will end but without affecting the rights or remedies of either party against the other in respect of any previous breach of any of the covenants or conditions in this Lease.

8.4 The Landlord shall refund to the Tenant any yearly rent and Service Charge paid pursuant to clause 8.2(a) paid in advance by the Tenant in respect of any period after the Break Date within 14 days of the Break Date.

8.5 Time is of the essence as to all the dates and periods referred to in this clause 8.

Executed and delivered as a deed on (but not before) the date of this document.

SCHEDULE 1

Premises rights and exceptions

Part 1
The Premises

All those Premises on the second and third floors of the Building shown edged red on Plan 1 and Plan 2.

1. The Premises include:

   (a) all internal walls floors and ceilings (including any raised floors suspended ceilings and the voids below and above them and all light fittings);

   (b) all internal cladding plasterwork and decoration and all floor screeding and finishes;

   (c) all doors door frames equipment fitments and any glass in the doors;

   (d) all internal windows and other lights and the frames glass equipment and fitments relating to such windows and lights;

   (e) all Conducting Media within and exclusively serving the Premises except where they form part of the Excluded Plant or Common Media;

   (f) all Landlord's fixtures and fittings (except where they form part of the Common Media or the Excluded Plant) including but without limitation the following:

      (i) electrical services for power lighting and telecommunications;

      (ii) drainage and water services;

      (iii) gas services;

      (iv) fire protection including sprinkler systems (if any);

      (v) distribution trunking ducting and conduits for electrical telephone and other communication services; and

      (vi) carpets;

   (g) all improvements and additions made to the Premises; and

   (h) all tenant's fixtures.

2. The Premises do not include:

   (a) the Main Structure but subject to paragraphs 1(c) and 1(d) of this Part 1 of this Schedule 1;

   (b) the airspace within any service risers that run through the Premises; and

   (c) the Excluded Plant.

Part 2
Rights granted

1. The right in common with all others having similar rights from time to time:

   (a) of unlimited access and passage to and from the Premises along and through the common accessways leading to and the common entrance staircases and passages of the Building and by means of the lifts in it;

   (b) of free passage of services from and to the Premises through the Common Media;

   (c) of support and protection from the Building and the Common Parts;

   (d) to use any bicycle parking, showers, lockers and changing area facilities within the basement (or such other part of the Building as may be designated by the Landlord) of the Building designated by the Landlord for use by the tenants of the Building and lavatories in the Building. Any showers and bicycle parking shall be available to use on a first come first served basis. Any lockers shall be designated by the Landlord on a pro rata (per square foot) basis;

   (e) at the cost of the Tenant in relation to such use (such proper and reasonable cost to be determined by the Landlord acting reasonably) an exclusive right to use the Roof Garden Terrace on not more than three occasions during each year of the Term (or such increased number as may reasonably be approved by the Landlord such approval not to be unreasonably withheld or delayed) on a "first come first served basis" out of Reception Hours subject to providing the Landlord with not less than 21 days' written notice and provided that exclusive use of the Roof Garden Terrace has not already been reserved by another tenant of the Building or by the Landlord on such date together with a non-exclusive right to use (at no cost to the Tenant other than those covered under the Service Charge) the Roof Garden Terrace on other occasions during the Reception Hours and (where it is not being exclusively used by another tenant in the Building) out of Reception Hours and in accordance with the Landlord's Regulations regarding the Roof Garden Terrace, together with rights to access the same along and through common accessways, entrances, staircases and passages of the Building heading to the Roof Garden Terrace;

   (f) to display the name of the Tenant (and any undertenant) on the Landlord's indicator board in the entrance lobby in the Building in the Landlord's house style and (subject to a maximum of one line for each floor of the Building) and outside the rear entrance to the Premises in a form reasonably approved by the Landlord (such approval not to be unreasonably withheld or delayed); and

   (g) to use a fair proportion of the riser space allocated to tenants for their use within the Building that the Landlord has reasonably designated for the purpose of installing and running new Conducting Media exclusively serving the Premises,

   PROVIDED THAT the rights at paragraphs (d) and (e) above may be suspended or withdrawn for such little time as reasonably necessary for the Landlord to carry out repairs or alteration to the Building.

2. Subject to the Tenant complying with paragraphs 17.1(b), 17.1(c) and 17.1(d) of Schedule 3, the right to erect and maintain wireless network equipment, television aerials and satellite dishes and plant not exceeding two metres in height in the Plant Area, of a size and design, and with connections to the Premises, approved in advance by the Landlord (such approval not to be unreasonably withheld or delayed) subject to the Tenant (and free of any expense to the Landlord):

(a) before commencing any works on the Plant Area obtaining all necessary statutory and other regulatory consents;

(b) obtaining all necessary wayleave or other agreements with the relevant equipment providers on terms reasonably acceptable to the Landlord;

(c) keeping such plant, equipment, aerials and dishes in good repair and condition;

(d) removing such plant and equipment from the Plant Area on assignment of the Lease (if the assignee confirms that it has no use for such plant and equipment) or on expiry or determination of the Term (whichever is the sooner) and making good all damage caused to the Building by such removal to the reasonable satisfaction of the Landlord;

(e) on not less than 14 days' notice (and subject to the Landlord providing an alternative location) from the Landlord temporarily removing the plant and equipment to allow the Landlord to carry out inspection maintenance and repair of the Plant Area; and

(f) on not less than 21 days' notice from the Landlord permanently relocating the plant and equipment to another area on the roof of the Building in a position previously reasonably approved by the Landlord,

provided that the Tenant will not in the exercise of the rights hereby granted cause any annoyance inconvenience disturbance or legal nuisance to the Landlord or any other tenant or occupier of the remainder of the Building.

3. If any of the equipment, aerials, dishes and plant installed in the Plant Area by the Tenant causes a legal nuisance disturbance or annoyance to the occupiers of any adjoining premises the Landlord may serve on the Tenant notice in writing requiring the Tenant to remove such equipment, aerials, dishes and plant to an alternative suitable location approved by the Landlord (acting reasonably) and within one month of the date of the notice the Tenant shall remove the equipment, aerials, dishes and plant to such approved alternative suitable location and make good any damage caused by such removal to the reasonable satisfaction of the Landlord's Surveyor unless the Landlord's Surveyor shall reasonably agree with the Tenant (at the cost of the Tenant) to make alterations to the equipment, aerials, dishes and plant that result in the cessation of such legal nuisance disturbance or annoyance.

Part 3
Exceptions and reservations

1. All rights of light or air to the Premises that now exist or that might (but for this reservation) be acquired over any other land.

2. The free passage of services through the Common Media which are now or may at any time be within the Premises.

3. The right to enter the Premises for the purpose of:

(a) anything properly connected with the provision of Services;

(b) adding to inspecting cleansing maintaining modernising repairing replacing or altering the Common Media;

(c) erecting scaffolding and/or building on under or into the Building;

(d) preparing any EPCs undertaking or reviewing any measurements required for any Environmental Rating System or undertaking an air conditioning inspection and for such purposes the right to carry out the necessary tests on Conducting Media, Excluded Plant and any other plant and machinery in the Premises;

(e) ascertaining whether the covenants and conditions on the Tenant's part of the Lease have been observed;

(f) to perform any of the covenants and conditions on the Landlord or exercise any rights set out in Part 3 to this Schedule;

(g) to carry out repairs, remove any unauthorised alteration or carry out any other works which the Tenant should have carried out in accordance with the Tenant's covenants in this Lease;

(h) to carry out or permit to be carried out repairs, maintenance, decoration, replacement, removal and cleaning of any parts of the Building (excluding the Premises) or any adjoining or neighbouring premises which cannot be reasonably carried out without access to the Premises;

(i) to protect the security of the Premises or prevent any easement being acquired over any part of the Building; and

(j) to show the Premises or the Building to a potential purchaser or in the last six months of the Term a tenant.

4. All rights of entry in Schedule 3.

5. In exercising its rights of entry under this Lease the Landlord will:

(a) give the Tenant reasonable prior written notice of not less than 48 hours (except in the case of emergency, when the Landlord must give as much notice as may be reasonably practicable);

(b) observe the Tenant's reasonable requirements (but where that includes being accompanied by the Tenant's representative the Tenant must make that representative available);

(c) observe any specific conditions to the Landlord's entry set out in this Lease;

(d) cause as little physical damage as is reasonably practicable; and

(e) repair any physical damage that the Landlord causes as soon as reasonably practicable to the reasonable satisfaction of the Tenant.

SCHEDULE 2

The Encumbrances

The matters contained or referred to in title number LN38304 as at 15 November 2017 at 15:33:37 insofar that they subsist and relate to the Premises.

SCHEDULE 3

Covenants by the Tenant

1 **PAYMENT OF RENTS**

To pay the Rent when stipulated without deduction or set-off and by electronic transmission of funds unless the Landlord reasonably requires otherwise.

2 **OUTGOINGS**

2.1 To pay and indemnify the Landlord against all Outgoings in relation to the Premises.

2.2 In the last 12 months of the Term to pay all non-domestic rates in full and not to claim empty property relief.

2.3 Within 14 days of written demand, to pay to the Landlord or as the Landlord may direct a fair and reasonable proportion of the Energy Costs attributable to:

(a) the supply of electricity and gas to the Premises alone; and

(b) the supply of electricity and gas to the Premises and any other parts of the Building to the extent that those Energy Costs do not form part of the Service Charge.

2.4 To reimburse the Landlord for loss of relief from non-domestic rates for unoccupied property which would have been available to the Landlord in respect of vacancy of the Property after the termination of this Lease but for the allowance of relief to the Tenant for vacancy commencing before the termination of this Lease.

3 **VAT**

3.1 To pay within 14 days' of written demand and subject to receipt of a valid VAT invoice VAT:

(a) chargeable on goods and services supplied by or on behalf of the Landlord; and

(b) paid or payable by the Landlord in respect of sums which the Landlord is entitled to recover from the Tenant which do not fall within Schedule 3 paragraph 3.1(a).

3.2 Not do anything that would result in the disapplication of the option to tax in respect of the Landlord's interest in the Building.

4 **INTEREST ON ARREARS**

4.1 If the Rent reserved by this Lease and any VAT on them is not paid within 14 days of the due date to pay to the Landlord Higher Rate Interest on them.

4.2 If collection of rent is suspended for material breach of covenant the Tenant must when the breach has been made good to the Landlord's reasonable satisfaction or when this Lease is forfeited (as the case may be) pay Higher Rate Interest in addition to the arrears of rent then due.

5 **DECORATION**

5.1 To decorate the Premises whenever necessary and also in the six months before the end of the Term (but no more than once in any two year period) in a proper and workmanlike manner and with appropriate materials of good quality to the reasonable satisfaction of the Landlord and in the final year to obtain the Landlord's consent to any changes to the colour or redecoration of the Premises.

5.2 Not to decorate any door or window facing the Common Parts or forming part of the exterior of the Building except in a colour or colours approved by the Landlord (such approval not to be unreasonably withheld or delayed).

6 **REPAIRS**

6.1 Subject to paragraph 6.5 of this Schedule 3 and paragraph 3 of Schedule 4 to keep the Premises in good and substantial repair and condition and clean excluding damage by an Uninsured Risk or Insured Risks except to the extent insurance moneys are irrecoverable due solely or in part to any act or default of the Tenant or any person deriving title under the Tenant or any of their respective agents employees licensees or contractors.

6.2 Without prejudice to paragraph 6.1 of this Schedule 3 to have all fixtures and fittings which comprise plant or equipment inspected and serviced at regular intervals by appropriately qualified contractors and to keep full service records with such records to be available at the Premises for the Landlord's inspection and to replace any fixtures or fittings (other than the Tenant's trade fixtures and fittings) that are lost or become beyond economic repair during the Term.

6.3 To clean the Premises (including the inside of the windows at regular intervals) and keep it tidy.

6.4 To keep the carpet tiles or carpet fitted in the Premises clean and in good repair order and condition and to make good all damage thereto howsoever arising (including accidental damage) and to replace with similar quality carpet tiles of at least equal value all such parts thereof as may at any time be destroyed or damaged as to be incapable of complete reinstatement to its former condition and not without the written consent of the Landlord to remove any of the said carpet tiles or carpet from the Premises except for the purpose of cleaning or necessary repairs and without prejudice to the generality of the foregoing within one month prior to the expiration or sooner determination of the Term to replace the carpet or carpet tiles on the Premises with (or if there are no carpet tiles or carpet on the Premises then to install on the Premises) good quality carpet tiles or (at the discretion of the Landlord) carpet of a type to be specified by the Landlord provided that the value of such carpet or carpet tiles shall not be less in value than £25 per square metre (excluding VAT) with due allowance for inflation after the date of this Lease.

6.5 Not to repair or replace any part of the Excluded Plant.

6.6 Upon becoming aware of the same to notify the Landlord immediately of any defect in the Excluded Plant, so that the Landlord can repair the same in accordance with the terms of this Lease.

6.7 Where beyond economic repair to replace any door or window referred to in paragraph 5.2 requiring to be replaced under paragraph 6.1 of this Schedule 3 with one of similar quality and appearance or otherwise as approved by the Landlord (approval not to be unreasonably withheld or delayed).

6.8 In carrying out all repairs and any other works under this Lease to use all reasonable endeavours:

(a) to do so in a sustainable manner;

(b) to treat and maintain all materials in accordance with their manufacturers' instructions and recommendations; and

(c) to minimise any material and adverse effect on any Environmental Rating System and/or any Environmental Rating.

7 **ENTRY BY LANDLORD TO VIEW AND REQUIRE TENANT TO REPAIR**

7.1 To permit the Landlord at all reasonable times after reasonable notice of not less than 48 hours (except in an emergency) to enter the Premises to view their condition and to give notice to the Tenant of any unauthorised alterations or any defects which are the Tenant's responsibility.

7.2 Within two months after receipt of any such notice (or sooner if reasonably necessary) to repair and make good such defects or remove such alterations to the reasonable satisfaction of the Landlord's Surveyor.

7.3 In case of default to permit the Landlord to enter and execute such works and to pay to the Landlord with 14 days of written demand and as a debt all expenses incurred with Higher Rate Interest from the date of expenditure.

8 **YIELDING UP**

8.1 At the end of the Term:

(a) to yield up the Premises with vacant possession in accordance with the Tenant's obligations with (subject to paragraphs 8.1(c) and 8.1(d) of this Schedule 3) all additions and improvements;

(b) to reinstate the Premises to the layout, state and condition as set out in the Category A Specification and with new carpeting as provided for in paragraph 6.4 of this Schedule 3;

(c) not to remove any alterations which have been carried out during the Term which improve the energy or water efficiency of the Premises and/or any Environmental Rating unless such removal is reasonably required by the Landlord;

(d) (subject to paragraph 8.1(c) above or if reasonably required by the Landlord) at the Tenant's expense to remove from the Premises any alterations or additions made by the Tenant or its predecessors in title during the Term or anyone claiming title to the Premises through or under the Tenant or any of them either before the commencement of or during the Term;

(e) to make good to the reasonable satisfaction of the Landlord any damage caused to the Premises by such removal;

(f) to give up all keys to the Premises to the Landlord;

(g) to remove all signs erected by the Tenant on or near the Premises and to make good as soon as reasonably practicable any damage caused;

(h) to deliver to the Landlord the original health and safety file relating to the Premises (properly completed) and all assessments reports and surveys carried out and relating to the Premises (whether carried out pursuant to a statutory requirement or otherwise) and all manuals working drawings and service records (held by the Tenant) relating to plant and equipment remaining at the Premises (including all such materials relating to installations of the Tenant which are to remain at the Premises) and to assign to the Landlord (if reasonably required) the benefit of any guarantees or warranties which are capable of assignment and which relate to plant and equipment remaining at the Premises;

(i) to deliver to the Landlord this Lease and to remove from any register of title affected any entry relating to this Lease or to any rights granted by this Lease and (without prejudice to its obligation to remove any such entry) to sign or execute such application or document as the Landlord may reasonably require to ensure such removal;

(j) to secure the Tenant's covenant in paragraph 8.1(i) of this Schedule 3 the Tenant irrevocably appoints the Landlord (at the end of the Term only) as attorney of the Tenant and in its name (and with power to appoint the Landlord's solicitor as substitute attorney) to make any application or sign or execute any document which has been required under paragraph 8.1(i) of this Schedule 3 but only if the Tenant is in breach of that paragraph.

8.2 In case of default the Landlord may do anything necessary to comply with the requirements in paragraph 8.1 if the Tenant has failed to comply with such requirements within a reasonable time on written notice from the Landlord.

8.3 To pay to the Landlord within 14 days of written demand all expenses so incurred in accordance with paragraph 8.1 with Higher Rate Interest from the date of expenditure.

9 TO NOTIFY LANDLORD OF STATUTORY NOTICES

9.1 As soon as reasonably practicable following receipt of any permission notice direction order certificate assessment or proposal relevant to the Landlord's interest in the Premises given or issued under any act of parliament to produce a copy to the Landlord.

9.2 At the request of the Landlord to make (or join with the Landlord in making) such objections or representations as the Landlord reasonably requires in respect of any such permission notice order certificate assessment or proposal at the Landlord's cost and provided that such objection and representation does not affect the Tenant's use and enjoyment of the Premises.

10 COMPLIANCE WITH STATUTORY AND INSURANCE REQUIREMENTS

10.1 At the Tenant's own expense to comply with (except where the Landlord is required to comply with such obligations under the Lease):

(a) all legislation from time to time in force;

(b) the requirements of the Landlord's insurers notified to the Tenant in writing;

(c) the reasonable requirements of the Landlord relating to the Premises its use or the rights granted by this Lease.

10.2 Not to do anything which may result in the Landlord under any statute incurring or having imposed upon it any liability.

10.3 In default the Landlord may enter the Premises (if the Tenant fails to rectify such default within a reasonable period of time following notice from the Landlord) and do anything reasonably necessary to ensure compliance with this paragraph 10.

10.4 To pay to the Landlord within 14 days of written demand all expenses so incurred as a debt with Higher Rate Interest from the date of expenditure.

10.5 If required by the Landlord at the Tenant's cost to connect to the Landlord's reasonable satisfaction any fire alarm system for the Premises into any fire alarm system for the Building.

11 COMPLIANCE WITH TOWN AND COUNTRY PLANNING REQUIREMENTS

11.1 To comply with the Planning Acts in relation to the Tenant's use and occupation of the Premises.

11.2 Not to make an application for planning permission in relation to the Premises or to raise any notices in respect of any applications without the consent of the Landlord (such consent not to be unreasonably withheld or delayed) if the application relates to a matter for which the Landlord cannot unreasonably withhold or delay its consent under the Lease.

11.3 Not to implement any planning permission relating to the Premises without the Landlord's consent (such consent to be unreasonably withheld or delayed where it has given consent to the application for such planning permission).

11.4 Unless the Landlord otherwise directs to complete before the end of the Term any works stipulated to be carried out to the Premises by a date subsequent to the end of the Term as a condition of any planning permission granted for any development begun before the end of the Term.

11.5 When requested to produce such reasonable evidence as the Landlord reasonably requires to satisfy itself the provisions of this paragraph have been fully complied with.

12 ENTRY BY THE LANDLORD AND OTHERS TO REPAIR AND FOR OTHER PURPOSES

12.1 To permit the Landlord and occupiers of any adjoining premises or their workpeople to enter the Premises upon reasonable notice and not less than 48 hours (except in the case of emergency) for the purpose of:

(a) inspecting or executing repairs or alterations to or upon such adjoining premises or the Building;

(b) inspecting maintaining repairing or replacing the Excluded Plant;

(c) decorating the Common Parts and the exterior of the Building (where such works cannot otherwise reasonably be carried out or be carried out without disproportionate expenditure by the Landlord);

(d) doing anything the Landlord reasonably considers desirable for the performance of its covenants in this Lease or to third parties or the provision of the Services;

(e) inspecting or surveying the Premises for valuation (but no more than once every year) letting or sale purposes or to prepare any schedule or inventory to the Premises or the Building; and

(f) doing anything reasonably incidental to the repair maintenance management environmental improvement or security of the Building or the performance of the Landlord's legal duties and compliance with proper practice in relation to health and safety or otherwise,

subject to the person exercising such rights causing as little inconvenience and disturbance to the Tenant and making good any damage caused.

12.2 To permit all persons with authority from the Landlord upon reasonable notice not less than 48 hours at all reasonable times in the daytime to enter and view the Premises for the purposes of selling or in the last six months of the term for the purposes of reletting.

13 COSTS ON BREACH

To pay on demand all costs, charges and expenses (including enforcement officers and professional fees) incurred by the Landlord:

(a) resulting from any breach by the Tenant of any of its obligations under this Lease;

(b) in or in contemplation of any proceedings under sections 146 and/or 147 of the Law of Property Act 1925 notwithstanding forfeiture is avoided otherwise than by relief granted by the court;

(c) in the recovery or attempted recovery of arrears of any rent due under this Lease; and/or

(d) in the preparation and/or service of any notice or schedule relating to the condition of the Premises whether during or within six months after the end of the Term but if after the end of the Term only in respect of wants of repair occurring during the Term.

14 **COMMON PARTS**

Not to obstruct the Common Parts with any articles or goods and to keep all Common Parts clear and tidy of the Tenant's articles, goods and rubbish.

15 **NOT TO INTERFERE WITH COMMON MEDIA**

Not to overload damage or interfere with:

(a) the Common Media or the Conducting Media;

(b) the plant and machinery and landlord's fixtures and fittings in the Common Parts;

(c) any sprinkler or fire alarm system serving the Premises; or

(d) the Excluded Plant.

16 **AS TO ALTERATIONS**

16.1

(a) Not to carry out any structural alterations to the Premises.

(b) Subject to paragraph 16.2 not without the consent of the Landlord to make any alterations or additions to the Premises (such consent not to be unreasonably withheld or delayed).

(c) If paragraph 16.3 is not complied with the Landlord may refuse or withdraw consent under this paragraph 16.1.

16.2 Notwithstanding the provisions of paragraph 16.1 the Tenant may install and remove internal demountable partitions (together with associated light switches and floorboards) without the Landlord's consent provided that:

(a) the Tenant shall not (in the reasonable opinion of the Landlord):

(i) adversely affect the performance or life cycle of; or

(ii) damage or carry out any alterations to

the Common Parts, the Conducting Media, Common Media or any other common service facilities plant equipment or systems serving or used in the Building; or

(iii) in any way affect the external appearance of the Building; or

(iv) alter the Conducting Media or the Common Media; or

(v) adversely affect the EPC rating for the Building; or

(vi) in any way overload the Conducting Media or the Common Media;

(b) such alterations do not and are not likely to adversely affect the provision by the Landlord of the Services within the Building;

(c) the Tenant complies with the obligations in paragraph 16.3; and

(d) details, specifications and drawings of any works undertaken pursuant to this paragraph 16.2 of this Schedule 3 are provided to the Landlord within one month of completion of the same.

16.3 In making any alterations or addition to the Premises the Tenant must comply with any statute in relation to environmentally responsible property management.

16.4 If alterations or additions are made to notify the Landlord in writing as soon as reasonably practicable following completion of the cost of the works for insurance purposes.

16.5 If the Tenant carries out or engages others to carry out any work at the Premises to which the CDM Regulations apply to comply with their requirements and enter into such covenants as the Landlord reasonably requires in relation to such regulations.

16.6 To keep a copy of all necessary health and safety files available at the Premises for inspection on reasonable notice not less than 48 hours by the Landlord and third parties.

16.7 Where the Tenant is making alterations which are permitted by the Landlord which may cause a material reduction in the energy efficiency of the Premises or which have a material effect on:

(a) any Environmental Rating System and/or any Environmental Rating; or

(b) the efficiency of the use of energy or water or waste efficiency within the Premises or the Building,

to provide such information as the Landlord reasonably requires to enable the Landlord to ascertain the effects of such alterations and to have due regard to and where reasonable implement any necessary reasonable requirements the Landlord makes to minimise any such material and adverse effect which the alterations may otherwise have.

16.8 In making alterations which are permitted by the Landlord or by the provisions of paragraph 16 the Tenant shall:

(a) do so in a sustainable manner; and

(b) treat and maintain all materials in accordance with their manufacturers' instructions and recommendations.

16.9 The Tenant shall not carry out any alterations to the Premises that would have an adverse effect on the Environmental Rating.

17 AERIALS AND SIGNS

17.1 Not to:

(a) place or affix any sign signboard fascia placard bill notice or other notification whatsoever to or upon:

(i) the windows or inside the Premises so as to be visible from the outside; and

(ii) the entrance doors of the Premises except for the name of the Tenant and any permitted occupiers on the doors in materials and a style and manner approved by the Landlord (such approval not to be unreasonably withheld or delayed);

(b) install Electronic Communications Apparatus or apparatus relating to Wireless Data Services except where intended only to serve the lawful occupier's business at the Premises and only then with the Landlord's prior written consent (such consent not to be unreasonably withheld or delayed);

(c) operate any Electronic Communications Apparatus so as to interfere with the lawful use of Electronic Communications Apparatus or the provision of Wireless Data Services elsewhere in the Building or on any adjoining premises;

(d) grant any rights pursuant to the Telecommunications Act 1984 without the prior consent of the Landlord (such consent not to be unreasonably withheld or delayed). When making any application for such consent the Tenant shall give full details to the Landlord of any works to be carried out prior to or as a result of the grant of such rights,

PROVIDED THAT if any equipment, sign, Electronic Communications Apparatus or Wireless Data Services signs shall be placed or displayed in breach of the provisions of this paragraph and shall not be removed within 14 days of service on the Tenant of a written notice requesting their removal to permit the Landlord or its agents to enter the Premises and remove such signs, Electronic Communications Apparatus or Wireless Data Services and pay to the Landlord within 14 days of written demand the proper and reasonable costs incurred in doing so.

17.2 The Tenant shall not be granted any naming rights in respect of the Building or the Premises and the Tenant shall use the postal address for the Building as notified to it by the Landlord.

18 NOT TO STRAIN FLOORS AND CEILINGS

Not to impose any strain on the floors and ceilings of the Premises beyond that which they were designed to bear.

19 USE

19.1 Not to use the Premises or any part of them otherwise than as for the Permitted Use.

19.2 Nothing in this Lease constitutes a warranty that the above use complies with the Planning Acts.

20 REGULATIONS

20.1 To observe the Landlord's Regulations.

20.2 Not to store in the Premises anything which is specially flammable, explosive or combustible (save such items required for the Tenant's use of the Premises).

20.3 Not to emit any smoke, fumes or smells from the Premises.

20.4 Not to store anything outside the Premises other than the equipment permitted under paragraph 2 of Part 2 of Schedule 1.

20.5 Not to obstruct any area used in common with others.

20.6 Not to do anything that blocks the Conducting Media or makes them function less efficiently including any blockage or damage to any drains, pipes or sewers by virtue of any waste, grease or refuse deposited by the Tenant.

20.7 Not to cook food on the Premises.

20.8 In case of default the Landlord may enter (if the Tenant fails to rectify any breach within a reasonable period) and do anything reasonably necessary to comply with the requirements of this paragraph and to pay to the Landlord on demand all expenses so incurred with Higher Rate Interest from the date of expenditure.

21 PROHIBITED USES

Not to:

(a) use the Premises in connection with the sale of the timeshares.

(b) use the Premises (or the Roof Garden Terrace, the showers and changing facilities in the Building or any of the Common Parts) for any illegal purpose or cause any legal nuisance or damage to the Landlord or the occupiers of the Building or to the owners, occupiers or tenants of any adjoining or neighbouring premises.

22 NOT TO PERMIT ENCROACHMENTS

22.1 Not to:

(a) stop up darken or obstruct any windows or light belonging to the Premises; or

(b) permit any encroachment or easement to be made or acquired which causes or might cause damage to the Landlord or any of its tenants.

22.2 If any encroachment or easement is or is attempted to be made or acquired the Tenant will give notice to the Landlord as soon as it becomes aware and at the Landlord's cost do whatever is reasonably required to prevent such encroachment or acquisition.

23 ALIENATION

23.1 **Restrictions on alienation**

Not to:

(a) part with or share possession or occupation of the whole or any part or parts of the Premises or charge or mortgage the whole or any part or parts of the Premises save in accordance with the provisions of this paragraph 23; or

(b) grant to any third parties any rights over the Premises except by way of an assignment, underlease or charge of the whole of the Premises in accordance with the provisions of this paragraph 23.

23.2 **Consent of the Landlord**

Neither the Tenant nor any person deriving title under the Tenant shall assign or underlet the whole of the Premises without the Landlord's consent (such consent not to be unreasonably withheld or delayed).

23.3 **Assignments**

(a) Not to assign any part of the Premises (as distinct from the whole).

(b) If requested for consent to an assignment of whole the Landlord will be entitled (for the purposes of section 19(1A) of the Landlord and Tenant Act 1927) to impose (in addition to any other condition or conditions the incorporation of which would be reasonable) all or any of the matters set out in paragraph 23.3(c) as a condition of its consent.

(c) The Landlord shall require:

(i) the execution by the Tenant and delivery to the Landlord prior to the assignment in question of an Authorised Guarantee Agreement;

(ii) the Guarantor (not here including a former tenant) to enter into contracts with the Landlord guaranteeing that the Tenant will comply with its obligations comprised in the Authorised Guarantee Agreement;

(iii) the payment to the Landlord of all Rent and other sums which have fallen due under the lease prior to the date of the assignment provided that such sums have been demanded in writing 21 days prior to the date of the application for such assignment and such sums remain undisputed;

(iv) that any intended assignee procures a surety or sureties for such assignee who must be reasonably acceptable to the Landlord and covenants with the Landlord as stated in Schedule 8 Parts 1 and 2; and

(v) the intended assignee deposits with the Landlord a security for the Tenant's obligations under this Lease a rent deposit equal to 6 months' rent and on terms of a deed in such form as the Landlord may reasonably require.

(d) The Tenant may assign the whole of the Premises to a Group Company with the Landlord's consent (such consent not to be unreasonably withheld or delayed) and subject otherwise to complying with the provisions of this Clause 23 save that the Landlord may refuse consent to any assignment where the Tenant wishes to assign this Lease to:

(i) any company that, at the date of assignment is a Group Company of the Tenant:

(1) and in the opinion of the Landlord, the financial strength of the proposed assignee when assessed together with any proposed guarantor or other security offered is not at least equivalent to the financial strength of the Tenant and its guarantor (if any); or

(2) the proposed guarantor for the Group Company is the guarantor for the Tenant;

(ii) an existing guarantor of the Lease as at the date of application for consent to assign the Lease.

(e) **Underletting**

(i) Not to underlet any part of the Premises (as distinct from the whole or a Permitted Part).

(ii) Not to underlet the whole of the Premises or a Permitted Part of the Premises without the Landlord's consent (such consent not to be unreasonably withheld or delayed) except where the following conditions are fulfilled:

(1) any underlease whether mediate or immediate must:

a. be at not less than an open market rent at the time of grant without fine or premium;

b. contain a covenant by the undertenant not to assign underlet part with possession of or share possession or occupation of the whole or any part or parts of the subdemised premises or mortgage or charge the whole or any part or parts of the subdemised premises except by way of sharing occupation with a Group Company (as permitted under this Lease) or an assignment or charge of the whole of the subdemised premises;

c. contain a covenant by the undertenant not to assign or charge the whole or a Permitted Part of the subdemised premises without the consent of the Landlord such consent not to be unreasonably withheld or delayed;

d. except as to the payment of the rent first reserved under this Lease otherwise be on similar terms (mutatis mutandis) to the terms of this Lease save that where the underlease contains a valid agreement under section 38A of the 1954 Act to exclude the provisions of sections 24 to 28 of that Act such underlease need only otherwise be on similar terms as to user and alterations; and

e. be in a reasonable form approved by the Landlord prior to its grant such approval not to be unreasonably withheld or delayed.

(2) any underlease must contain a valid agreement under section 38A of the 1954 Act to exclude the provisions of sections 24 to 28 of that Act in relation to that underlease; and

(3) before the grant of any underlease the Tenant must procure a covenant from the undertenant with the Landlord to pay the rents and other sums reserved by the underlease (or if the underlease of a Permitted Part of the Premises, a fair proportion of them) and observe and perform the undertenant's covenants and the conditions in the proposed underlease and not to do or omit any act or thing which would or might cause the Tenant to be in breach of the Tenant's covenants in this Lease; and

(4) before the grant of any underlease but subject to paragraph 16 of this Schedule 3, the Tenant must carry out all works to the Premises that are required by statute for the Tenant lawfully to grant an underlease.

(iii) The Tenant shall:

(1) not consent to or participate in any variation to any underlease without the Landlord's consent such consent not to be unreasonably withheld or delayed;

(2) enforce all the covenants and obligations of the undertenant under any underlease.

(f) **Sharing with Group Companies**

Notwithstanding the above, the Tenant may share occupation of the whole or any part or parts of the Premises with any Group Company of the Tenant on condition that:

(i) the interest so created is no more than a tenancy at will; and

(ii) the right of any company to occupy the Premises or any part or parts of it immediately ends upon such company ceasing to be a Group Company.

(g) **To supply information**

Within 14 days of demand to give the Landlord particulars of any derivative interest in the Premises, including the rents payable and such other information and copy documents as the Landlord reasonably requires at the Tenant's cost if this paragraph is not invoked more frequently than once a year but otherwise the Landlord is to bear the Tenant's reasonable costs of compliance.

(h) **Charging**

The Tenant may charge the whole of the Premises to a genuine lending institution with the Landlord's consent (not to be unreasonably withheld or delayed) provided that no consent shall be required in respect of a floating charge over the Tenant's business.

24 **REGISTRATION OF DEALINGS**

Within one month after any assignment or underletting or the assignment of an underlease or after any devolution by will or otherwise or mortgage or charge affecting the Premises to produce to the solicitor for the time being of the Landlord a certified copy of the deed or instrument effecting the same and pay his reasonable fee for registration being no more than £50.00 plus VAT.

25 **COSTS**

25.1 To pay all the Landlord's reasonable and proper costs fees and/or expenses incurred in connection with any request for a licence or consent pursuant to the terms of this Lease including where the request is withdrawn or the licence or consent is lawfully withheld except to the extent that consent is unlawfully refused or delayed.

25.2 To pay to the Landlord within 14 days of written demand all costs, fees and expenses incurred by the Landlord in carrying out works to the Premises to improve their Environmental Rating where the Tenant has consented to the Landlord doing so.

26 **ENERGY PERFORMANCE CERTIFICATES**

26.1 To comply with all statutory obligations from time to time:

(a) requiring the Tenant to provide an EPC to any third party or to the Landlord; and/or

(b) which relate to any Environmental Rating System.

26.2 If and to the extent that the Existing EPC remains valid (for the purposes of Regulation 9(2) of the Energy Performance of Buildings (England and Wales) Regulations 2012) to provide the Existing EPC in satisfaction of its obligations pursuant to paragraph 26.1.

26.3 If and to the extent that the Existing EPC is no longer valid (whether or not as the result of the Tenant's alterations) to notify the Landlord and to obtain any EPC required to be provided from an energy assessor nominated by the Landlord (acting reasonably).

26.4 To provide the Landlord with copies of all EPCs obtained by the Tenant whether or not obtained in accordance with this paragraph 26.

26.5 As soon as reasonably practicable following written demand to provide the Landlord with any information in relation to energy efficiency matters and EPCs as the Landlord reasonably requires at the Tenant's cost.

27 **INDEMNITY**

To indemnify the Landlord against all actions proceedings claims demands losses costs expenses damages and liability (including any liability for any injury to any person or damage to any land or other property) and any court or tribunal orders or awards arising from the breach non-observance or non-performance by the Tenant of its covenants and the conditions in this Lease (including, for the avoidance of doubt, any action, proceeding, claim, cost, expense, damage or liability relating to the Tenant's use of the Roof Garden Terrace) and/or by any act default or negligence of the Tenant or any person deriving title under the Tenant or their respective agents employees or licensees.

28 **ENCUMBRANCES**

To perform and observe the Encumbrances (by way of indemnity only) so far as they relate to the Premises.

29 **INSURANCE AND SERVICES**

To observe and perform the covenants in Schedules 6 and 7.

30 **GUARANTORS**

If any Guarantor suffers an Insolvency Event, or in the case of an individual, dies, the Tenant shall as soon as reasonably practicable procure that a replacement guarantor reasonably acceptable to the Landlord enters into a guarantee with the Landlord on the same terms as that Guarantor.

31 **DEFECTIVE PREMISES**

In respect of any defects in the Premises which might give rise to a duty or liability on the part of the Landlord under the Defective Premises Act 1972, any other statutory provision or at common law, the Tenant shall:

(a) give as soon as reasonably practicable notice in writing to the Landlord of the defects as soon as it becomes aware of them;

(b) display on the Premises any notice which the Landlord may reasonably require; and

(c) take any other action at the Landlord's cost which the Landlord may properly and reasonably require to discharge any such duty or liability.

32 **ENVIRONMENTAL OBLIGATION**

32.1 The Tenant shall not discharge or permit to be discharged any Hazardous Materials, oil, grease or any other deleterious materials into any Conducting Media serving the Premises or the Building or any adjoining or neighbouring premises.

32.2 The Tenant shall not do or omit to do anything that does or may cause any Hazardous Materials to escape, leak or be spilled or deposited on the Premises or the Building or to migrate to or from the Premises or the Building.

SCHEDULE 4

Covenants by the Landlord

1 **QUIET ENJOYMENT**

Subject to the Tenant paying the Rent reserved by and observing and performing the Tenant's covenants in this Lease the Tenant may quietly enjoy the Premises during the Term without any lawful interruption or disturbance from or by the Landlord or any person or persons lawfully or equitably claiming under or in trust for it.

2 **INSURANCE AND SERVICES**

To observe and perform its obligations in Schedules 6 and 7.

3 **PURSUIT OF THIRD PARTIES**

The Landlord shall use reasonable endeavours to enforce the rights and remedies which it has against third parties (including but not limited to the developer, the contractor, any sub-contractors and the professional team involved in the refurbishment of the Premises under the building contract dated 18 December 2014 and made between British Overseas Bank Nominees Limited and WGTC Nominees Limited in their capacity as nominees for and on behalf of National Westminster Bank plc as depositary and not otherwise of the M&G Property Portfolio (1) and Chorus Group Holdings Limited (2) (the "**Building Contract**")) in relation to any defect in the Premises which is due to any breach by such third party of its obligations and/or warranties to the Landlord. Should the Landlord fail to enforce such rights and remedies which it has against third parties within a reasonable time the Tenant may remedy or procure the remedying of such defect itself and the Landlord shall be responsible for the reasonable costs incurred by the Tenant in doing so. The obligations on the Landlord under this paragraph 3 of this Schedule 4 shall expire on the date of issue of the notice of completion of making good defects under the Building Contract.

SCHEDULE 5

Provisos Agreements And Declaration

1 **FORFEITURE**

Without limiting any other provisions in this Lease the Landlord may at any time re-enter the Premises and immediately on so doing this Lease will terminate absolutely but without prejudice to any rights of either party against the other in respect of any breach of any of the obligations in this Lease:

(a) if the Rent reserved by this Lease are unpaid for 21 days after becoming payable (whether, in the case of the rent first reserved under this Lease formally demanded or not); or

(b) if the Tenant is in breach of its obligations in this Lease; or

(c) the taking of any step in connection with any voluntary arrangement or other compromise scheme or arrangements for the benefit of any creditors of the Tenant or the Guarantor; or

(d) the making of an administration order in relation to the Tenant or the Guarantor; or

(e) if the Tenant or the Guarantor:

(i) (being a company or if in partnership) enters into liquidation whether compulsory or voluntary (other than for the purpose of reconstruction or amalgamation not involving a realisation of assets) or has a winding-up order made against it by the court or has a receiver appointed over all or any part of its assets or an administrator appointed or an administrative receiver; or

(ii) (being one or more individuals whether or not in partnership together) has a bankruptcy order made against him; or

(iii) becomes insolvent or unable to pay its or his debts or enters into any composition with its or his creditors or enters into a voluntary arrangement (within the meaning of sections 1 123 or 253 of the Insolvency Act 1986 or the Insolvent Partnerships Order 1994); or

(iv) has distress, sequestration, execution or any modem equivalent of these remedies levied on the Tenant's goods including any action taken for the recovery of rent arrears from the Tenant under Commercial Rent Arrears Recovery; or

(v) is struck off from the register or the relevant company ceases to exist;

(f) any event analogous to any of the above events occurs in any jurisdiction other than England and Wales.

2 **TENANT'S GOODS**

2.1 The Landlord is deemed to have been irrevocably appointed the Tenant's agent to store and/or dispose of all property belonging to the Tenant or to any third party not removed from the Premises by the Tenant in accordance with its covenants in Schedule 3 paragraph 8 and/or Schedule 6 paragraph 1.2(f).

2.2 The Tenant must:

(a) indemnify the Landlord against all costs and expenses and other liability incurred in respect of storage and/or disposal of such property and claims to such property by any third party; and

(b) pay on demand Higher Rate Interest on such costs and expenses from the date of expenditure.

3 LANDLORD'S RIGHT TO DEVELOP

3.1 The Tenant has no right which might restrict or prejudicially affect the future rebuilding alteration or development of any adjoining premises belonging to the Landlord (whether forming part of the Building or not) or to compensation for damage or disturbance caused by or suffered through any such rebuilding alteration or development.

3.2 Section 62 of the Law of Property Act 1925 will not apply to this Lease.

3.3 The flow of light to the Premises is and will be enjoyed with the Landlord's consent in accordance with section 3 of the Prescription Act 1832. Neither the enjoyment of that light and air nor anything in this Lease will prevent the exercise of any of the rights the Landlord has reserved out of this Lease. The Tenant must permit the exercise of these reserved rights without interference or objection.

3.4 The Tenant has no rights to enforce the benefit of any covenants, rights or conditions to which any other property within the Building or any adjoining premises is or are subject.

4 EXCLUSION OF STATUTORY COMPENSATION

The Tenant will not be entitled on quitting the Premises to any compensation under section 37 of the 1954 Act.

5 EXCLUSION OF LIABILITY

The Landlord shall not be liable to observe or perform any obligation on its part contained in this Lease (and the Tenant hereby releases the Landlord from time to time from all liability in respect of any breach or non-observance of any such obligation) after it has ceased to be entitled to the immediate reversion expectant upon the Term.

6 DISCLAIMER OF LIABILITY FOR USE OF COMMON BICYCLE SPACES, CHANGING AREAS AND ROOF GARDEN TERRACE

The Landlord will not be liable for loss or damage to any property or damage to any person or for the prevention of ingress to or egress from the basement (or any other part) of the Building or the Roof Garden Terrace caused by unauthorised use of the basement (or any other part of the Building) or Roof Garden Terrace.

7 ACCEPTANCE OF RENT IS NO WAIVER

Notwithstanding the demand for or acceptance of the Rent or any of the Rent by or on behalf of the Landlord with knowledge of a breach of any of the Tenant's covenants the Landlord's rights to forfeit this Lease on the ground of such breach shall remain in force and the Tenant shall not be entitled in any proceedings for forfeiture to rely on any such demand or acceptance as a defence.

8 CONCESSIONS FOR DUE DATES FOR PAYMENT

If the Landlord allows the Tenant to defer payment of any money due under this Lease then for all purposes in connection with this Lease (and in particular in relation to section 17 of the Landlord and Tenant (Covenants) Act 1995 that money shall be deemed to fall due on the later date allowed by the Landlord instead of the earlier date when it originally fell due.

9 **NOTICES**

Sections 196(1) and (4) of the Law of Property Act 1925 (as amended by the Recorded Delivery Service Act 1962) apply to all notices notification and certificates required to be given or served under this Lease.

10 **DATA PROTECTION ACT 1998**

For the purposes of the Data Protection Act 1998 or otherwise the Tenant and the Guarantor (if any) acknowledge that information relating to this tenancy will be held on computer and other filing systems by the Landlord or the Landlord's managing agent (if any) for the purposes of general administration and/or enforcement of this Lease and agree to such information being used for such purposes and being disclosed to third parties so far only as is necessary in connection with the management of the Landlord's interest in the insurance and/or maintenance of the Premises checking the credit worthiness of the Tenant and the Guarantor or the disposal or subletting of the Premises or the Building of which the Premises form part or is necessary to conform with recognised industry practice in the management and letting of property.

11 **VAT**

All sums payable under this Lease subject to VAT are tax exclusive sums.

12 **EXCLUSION OF SECTIONS 24-28 OF THE 1954 ACT**

12.1 The Landlord and the Tenant agree to exclude the provisions of sections 24-28 (inclusive) of the 1954 Act in relation to the tenancy to be created by this Lease.

12.2 The Tenant confirms that before it entered into the tenancy created by this Lease:

(a) the Landlord served on the Tenant a notice dated 12 January 2018 in relation to the tenancy created by this Lease (the "**Notice**") in a form complying with the requirements of Schedule 1 to the Order; and

(b) the Tenant, or a person duly authorised by the Tenant, in relation to the Notice made a statutory declaration (the "**Declaration**") dated 17 January 2018 in a form complying with the requirements of Schedule 2 to the Order.

12.3 The Tenant confirms that, where the Declaration was made by a person other than the Tenant, the declarant was duly authorised by the Tenant to make the Declaration on the Tenant's behalf.

12.4 The Landlord and the Tenant confirm that there is no agreement for lease to which this Lease gives effect.

13 **ENERGY PERFORMANCE CERTIFICATE**

The Tenant confirms that it has before the date of this Lease been provided with a copy of the Existing EPC.

14 **CO-OPERATION**

Without prejudice to any common law duty of co-operation the Landlord and the Tenant shall cooperate with each other by either party providing to the other whatever information each party reasonably requests relating to the energy and water consumption and waste management for or at the Premises.

15 **DISPUTE RESOLUTION PROCEDURE**

15.1 All Disputes shall be submitted to the Dispute Resolution Procedure.

15.2 The Expert shall be nominated by the parties jointly or in the absence of an agreed nomination shall be nominated by the president or other acting senior officer for the time being of the Royal Institution of Chartered Surveyors on the application of either party.

15.3 If the Expert refuses to act becomes incapable of acting or dies either party may require the appointment of a replacement Expert in the same manner as applied to the original appointment.

15.4 The Expert must act as an expert and not as an arbitrator and will be required to:

(a) give notice to both parties allowing them to submit to him within such reasonable time as he stipulates representations on the relevant issue accompanied (if either of them wishes) by a statement of reasons and professional valuations or reports of which copies are supplied to the other party; and

(b) permit each of the parties to make a submission in respect of the other's reasons valuation and reports (if any) provided under paragraph 15.4(a) of this Schedule 5; but

(c) neither party may without the consent of the other disclose to the Expert correspondence or other evidence to which the privilege of non-production ("**without prejudice**") properly attaches,

but the Expert will not be bound by any such submission or representations and he may make his determination as he thinks fit.

15.5 The determination of the Expert will be final and binding on the parties except in the case of manifest error.

15.6 The fees and expenses of the Expert including the cost of his nomination must be borne either as to the whole or in proportions as the Expert determines (but in the absence of determination they must be borne equally) and each of the parties must bear its own costs with respect to the determination of the Dispute by the Expert.

15.7 Either party may pay such costs of the Dispute Resolution Procedure required to be paid by the other as have been determined by the Expert if they remain unpaid for more than 21 days after they have become due and then recover these and any incidental expenses incurred from the defaulting party on demand.

16 ROOF SPACE

The Landlord (acting reasonably) shall manage the allocation of the roof space over which the Tenant is granted rights under Part 2 of Schedule 1 taking into account its own requirements and the requirements of other tenants and occupiers of the Building.

17 GOVERNING LAW AND JURISDICTION

17.1 This Lease shall be governed by and interpreted in accordance with English law.

17.2 The courts of England have exclusive jurisdiction in relation to any disputes between the parties arising out of or related to this Lease.

SCHEDULE 6

Insurance Provisions

1 **TENANT'S COVENANTS**

Insurance rent

1.1 The Tenant covenants with the Landlord to pay a sum equal to:

(a) the proportion the Landlord reasonably deems appropriate having regard to:

(i) any alterations or additions to the Building or any change of use of any part of it; or

(ii) information supplied to it by the Tenant pursuant to Schedule 3 paragraph 16.4,

of the cost the Landlord incurs in insuring against employer's liability and public liability risks in respect of the Building and insuring the Building against the Insured Risks including:

(iii) the preparation and settlement of any insurance claim;

(iv) the cost of complying with any requirements of the insurer; and

(v) valuation of the whole or any part of the Building (but not more than once in every three year period); and

(b) the whole of the cost as the Landlord incurs in insuring against four years' loss of the rent first reserved by this Lease and Service Charge arising from damage to the Building by any Insured Risks.

The insurance cover may include VAT and take due account of the effects of inflation and escalation of costs and the Landlord will be entitled to retain any commission paid to it.

Tenant's insurance obligations

1.2 The Tenant covenants with the Landlord:

(a) not to do or omit in or upon the Premises anything which may:

(i) render the Landlord liable to pay in respect of the Premises and/or the Building more than the rate of premium it might expect to pay in the open market to insure premises of a similar nature let on a similar basis against the Insured Risks; or

(ii) restrict or make void or voidable any policy for such insurance;

(b) to pay to the Landlord within 14 days of written demand any increase in the rate of premium and all expenses incurred in connection with any renewal of such policy rendered necessary by a breach of paragraph 1.2(a) of this Schedule 6;

(c) if:

(i) any part of the Premises or of the Building is destroyed or damaged by any Insured Risk; and

(ii) the insurance monies are wholly or partially irrecoverable by reason solely or in part of any act or default of the Tenant or any person deriving title under the Tenant or any of their respective agents employees or licensees; the Tenant must pay to the Landlord within 14 days of written demand a sum equal to the whole or a fair proportion (as the case may require) of the irrecoverable insurance monies;

(d) not to insure the Premises against any of the Insured Risks;

(e) upon becoming aware of the same to notify the Landlord promptly in writing of damage to the Premises by any Insured Risk;

(f) in the event of damage to the Premises by any Insured Risk or Uninsured Risk rendering them unfit for occupation or use (if so reasonably required by the Landlord) at the cost of the Tenant to remove from the Premises all property belonging to the Tenant or to any third party promptly following such damage or to indemnify the Landlord against the cost of doing so;

(g) in the event of damage to the Premises or the Building by any of the Insured Risks or Uninsured Risks to pay to the Landlord on demand a sum equal to the whole or proper proportion of any uninsured excess to which the insurance policy may be subject; and

(h) not to leave the Premises continuously unoccupied for more than 21 days without notifying the Landlord and providing such caretaking or security arrangements as the Landlord's insurers may require and/or the Landlord may reasonably require.

2 **LANDLORD'S COVENANTS**

To insure

(a) To keep insured the Building against loss or damage by the Insured Risks with an insurer of repute subject to such exclusions conditions limitations and uninsured excesses as the insurer may reasonably apply and at reasonable commercial rates generally available in the London insurance market for a building of this type size and location in a sum equal to:

(i) the full cost of reinstatement (taking into account any appropriate notification from the Tenant under Schedule 3 paragraph 16.4) including professional fees and the cost of removing all debris (excluding contents and stock debris) from the site of the Building, compliance with Local Authority requirements and other incidental expenses; and

(ii) four years' loss of the rent first reserved by this Lease and Service Charge.

(b) The Landlord must in relation to the insurance provide to the Tenant on written request (but no more than once in any 12 month period) a summary of the main terms of the Landlord's insurance cover.

To reinstate

(c) (i) Subject to any necessary labour and materials being and remaining available and to obtaining all necessary permissions and consents necessary to enable the Landlord to reinstate the Building or the Premises (as appropriate) or the access thereto (the "**Permissions**") which the Landlord must use reasonable endeavours to obtain as soon as possible to cause the insurance moneys received (except sums received for loss of rent first reserved and Service Charge) to be applied in clearing the site and reinstating the Building or a fair and reasonable proportion of those insurance moneys in relation to the Premises (as the case may be).

(ii) Any reference to reinstating the Building or the Premises in paragraphs 2, 3, 4 and 5 of this Schedule 6 means that the Building or Premises are reinstated substantially as they were before the relevant damage or destruction (but not so as to provide accommodation identical in layout if it would not be sensibly practicable to do so).

(iii) The Landlord's obligation to reinstate under this paragraph shall cease if the insurance shall be rendered void by reason of any act or default of the Tenant or any person deriving title under the Tenant or their respective agents servants licensees or contractors save to the extent that the Tenant has complied with its obligations in paragraph 1.2(c) of this Schedule 6.

(iv) The Landlord need not reinstate while prevented by any of the following:—

(1) failure by the Landlord to obtain the Permissions despite using all reasonable endeavours;

(2) the grant of any of the Permissions subject to a condition with which it would be unreasonable to expect the Landlord to comply or the planning or highway authority's insistence that as a pre-condition to obtaining any of the Permissions the Landlord must enter into an agreement with the planning or highway authority that would contain a term with which it would be unreasonable to expect the Landlord to comply;

(3) some defect in the site upon which the reinstatement is to take place so that it could not be undertaken or undertaken only at excessive cost;

(4) war act of God government action strike lock-out or any other similar circumstances beyond the control of the Landlord,

AND in such circumstances any insurance money (save any sums attributable to tenant's fixtures) will belong to the Landlord.

3 **SUSPENSION OF RENT**

3.1 If the Building or any part of it is so destroyed or damaged by an Insured Risk as to make the Premises or any part of them unfit for occupation access or use or inaccessible the yearly rent and the Service Charge or a fair proportion according to the nature and extent of the damage sustained will not be payable until the earlier of the date on which:

(a) either the Building or the Premises (as appropriate) have been reinstated so as to make the Premises fit for occupation or use (excluding fitting out and replacement of contents) and accessible; or

(b) the expiry of four years from the date of such damage,

(but this paragraph 3.1 of this Schedule 6 shall not apply to the extent that the Landlord's insurance has been vitiated or payment of any policy moneys refused owing to the act or default of the Tenant or any person deriving title under the Tenant or their respective agents employees licensees or contractors and/or the Tenant has not complied with its obligations in paragraph 1.2(c) of this Schedule 6).

3.2 If paragraph 3.1 of this Schedule 6 applies:

(a) the Landlord must refund to the Tenant a due proportion of the yearly rent and the Service Charge paid in advance; and

(b) on the date on which the Building is reinstated so as to make the Premises fit for occupation, use and accessible the Tenant must pay to the Landlord within 14 days of written demand the yearly rent for the period starting on the date they again become payable to but excluding the next quarter day.

4 **OPTIONS TO TERMINATE**

4.1 If the Building or a substantial part of it (whether including the Premises or not) is destroyed or damaged by an Insured Risk this Lease may be terminated by the Landlord giving to the Tenant (within 12 months after such destruction or damage) not less than six months' notice.

4.2 If for any reason outside the Landlord's control it proves impossible to commence rebuilding work within four years of the date of such damage or destruction the Landlord may by notice to the Tenant terminate this Lease and upon receipt by the Tenant of such notice the Term shall end.

4.3 If the Landlord has not completed the rebuilding work on site within three years and six months of the date of such damage or destruction so as to make the Premises fit for occupation or use (excluding fitting out and replacement of contents) and accessible then this Lease may be terminated by the Tenant giving to the Landlord six months' notice and upon the expiry of such notice the Term shall end.

4.4 If this Lease is terminated pursuant to paragraph 4.1, 4.2 or 4.3 the Landlord will be entitled to retain the whole of the insurance moneys for its absolute use and benefit and termination of the Term shall be without prejudice to any claim by any party in respect of any antecedent breach of any obligations under this Lease.

5 **UNINSURED RISKS**

5.1 For the purpose of this paragraph 5 of this Schedule:

(a) These provisions shall apply from the date on which any Insured Risk becomes an Uninsured Risk but only in relation to the Uninsured Risk.

(b) References to an Insured Risk becoming an Uninsured Risk shall without limitation include the application by insurers of an exclusion condition or limitation to an Insured Risk to the extent to which such risk thereby is or becomes an Uninsured Risk.

(c) The Landlord shall notify the Tenant in writing as soon as reasonably practicable after an Insured Risk becomes an Uninsured Risk.

5.2 If during the Term the Building or the Premises or a substantial part of them shall be damaged or destroyed by an Uninsured Risk so as to make the Premises or a substantial part of them unfit for occupation access or use or inaccessible:

(a) the yearly rent and the Service Charge or a fair proportion according to the nature and extent of the damage sustained will not be payable from the date of damage or destruction until the earlier of the date on which

(i) the Premises shall again be fit for occupation or use (excluding fitting out and replacement of contents) and made accessible; or

(ii) this Lease shall be terminated in accordance with paragraph 5.2(b) and paragraph 5.5 of this Schedule 6;

(b) the Landlord may within one year of the date of such damage or destruction serve notice on the Tenant confirming that it will reinstate the Building or the Premises or both of them as the case may be (a "**Reinstatement Notice**") so that the Premises shall be fit for occupation or use and made accessible and if the Landlord fails to serve a Reinstatement Notice within twelve months from the date of damage or destruction the Lease will automatically end on the date one year after the date of such damage or destruction.

5.3 Paragraph 5.2 shall not apply if an Insured Risk shall have become an Uninsured Risk owing to the act or default of the Tenant or any person deriving title under the Tenant or their respective agents, employees, licensees or contractors.

5.4 If the Landlord serves a Reinstatement Notice it shall use reasonable endeavours (subject to any necessary labour and materials being and remaining available and to obtaining all necessary permissions and consents necessary to enable the Landlord to reinstate the Building or the Premises (as appropriate) or the access thereto (the "**Permissions**") which the Landlord must use reasonable endeavours to obtain as soon as possible) to reinstate the Building and/or the Premises (as the case may be) and or access thereto as soon as reasonably practicable.

5.5 If the Landlord shall have served a Reinstatement Notice and such reinstatement has not been completed by the date three years and six months from the date of the damage at any time after that date the Landlord or the Tenant may terminate this Lease by serving not less than six months' notice on the other stating that it terminates this Lease and if by the end of such notice the Building or the Premises or both of them as the case may be have been reinstated so that the Premises are fit for occupation and use and are accessible the notice shall be void and this Lease shall continue in full force and effect.

5.6 Service of a Reinstatement Notice shall not oblige the Landlord to reinstate any alterations or additions not notified by the Tenant under Schedule 3 paragraph 16.4 to replace any Tenant's fitting out works or property belonging to the Tenant or any third party.

SCHEDULE 7

Service Charge Provisions

Part 1

1 **TENANT'S LIABILITY TO PAY SERVICE CHARGE**

1.1 The Tenant must pay to the Landlord the Service Charge.

1.2 The Service Charge is such proportion of the Landlord's Costs as the Landlord deems fair and attributable to the Premises in any Service Charge Period (as defined in paragraph 2.4 of this Schedule 7 Part 1) beginning or ending during the Term but without affecting the general operation of the Landlord's discretion:

(a) the proportion will be calculated primarily on a comparison of the Net Internal Area of the Premises with the aggregate Net Internal Area of the Lettable Areas; but

(b) if the Landlord properly and reasonably considers that such comparison is inappropriate the Landlord may adopt such other method of calculation as is fair and reasonable in the circumstances (including if appropriate the attribution of all such expenditure to the Premises).

1.3 The Landlord's Costs are the costs and expenses properly incurred by the Landlord of and incidental to the provision of the Services in or with respect to any Service Charge Period beginning or ending during the Term.

1.4 The Services are itemised in Parts 2 and 3 of this Schedule 7.

1.5 The Landlord's Costs the Service Charge and the provision of the Services will be calculated and dealt with in accordance with this Schedule 7.

2 **ADVANCE PAYMENTS ON PRELIMINARY BASIS**

2.1 The Service Charge will be paid by advance payments on each of the Rent Days and by additional payments required under paragraphs 3 and 4 of this part of this Schedule 7.

2.2 The amount of each advance payment will be equal to the last advance payment or otherwise be the amount the Landlord determines as likely to be equal in the aggregate to the Service Charge for the relevant Service Charge Period.

2.3 The Landlord will endeavour at least one month before the relevant Service Charge Period both to provide the Tenant with an estimate of the likely service charge expenditure and to notify the Tenant of the amount of each advance payment for the relevant Service Charge Period.

2.4 "**Service Charge Period**" means the period of 12 months from 1 August to 31 July in each year (or such other appropriate period of more or less than 12 months as the Landlord reasonably determines).

2.5 The Service Charge is deemed to accrue on a day to day basis in order to ascertain yearly rates and for the purposes of apportionment in relation to periods of other than one year.

3 **LANDLORD'S COSTS ACCOUNTS AND SERVICE CHARGE ADJUSTMENTS**

3.1 The Landlord will endeavour within four months after the end of each Service Charge Period to submit to the Tenant a statement duly certified by the Landlord the Landlord's Surveyor or the Landlord's managing agents (or audited by the Landlord's auditors if the Landlord so decides) giving a proper summary of the Landlord's Costs and the calculation of the Service Charge for the Service Charge Period just ended and the provisions in this Lease as to the giving of notices apply to the submission of the statement.

3.2 If the Service Charge as certified is less than the total of the advance payments (or the grossed up equivalent of such payments if made for any period of less than the Service Charge Period) then the Landlord will credit the balance against the next advance payment of Service Charge due from the Tenant or if the Term has ended will pay the balance due to the Tenant within 28 days after submission of the service charge statement to the Tenant.

3.3 If the Service Charge as certified is more than the total of the advance payments (or the grossed- up equivalent of such payments if made for any period of less than the Service Charge Period) then the Tenant will pay any sum due to the Landlord by way of adjustment within 14 days after the receipt of the Service Charge statement.

3.4 The Landlord shall permit the Tenant to inspect the vouchers and receipts for items included in the summary at paragraphs 3.1 of this Schedule 7 Part 1.

3.5 The provisions of this paragraph 3 will continue to apply after the expiry or earlier determination of this Lease in respect of any Service Charge Period then current.

3.6 Within 28 days after submission of a certified statement under paragraph 3.1 (time being of the essence) the Tenant may challenge it on the ground that it contains errors or is otherwise incorrectly drawn by giving to the Landlord notice to that effect but only if it has first made payment of the full amount due from the Tenant as shown on the statement and if so:

(a) both parties must use reasonable endeavours to resolve the relevant issue but if they cannot do so:

(i) the Dispute shall be referred to the Dispute Resolution Procedure;

(ii) any adjustments to the statement required to be made in consequence of the determination of the Expert must be made and any sum due to or payable by the Landlord must immediately (within 14 days of written demand in the case of any sum due to the Landlord) be paid or allowed as appropriate; and

(iii) Base Rate Interest must be paid or allowed in respect of the period during which the relevant amount has been underpaid or overpaid, but if not the Tenant’s right of challenge to that certified statement shall lapse.

4 **EXCEPTIONAL EXPENDITURE**

4.1 If the Landlord is required to incur or actually incurs heavy or exceptional expenditure which forms part of the Landlord’s Costs the Landlord will be entitled to recover from the Tenant the Service Charge in respect of the whole of that expenditure on the quarter day next following.

4.2 If funds collected by advance payments are insufficient to meet an immediate liability (and there is no reserve fund available to be applied to meet it) and the cause of the insufficiency is not vacancy of any Lettable Areas the Landlord may advance moneys (or borrow moneys for the purpose from reputable banks) at commercially competitive rates of interest and interest payable on the advance or the borrowing will form part of the Landlord’s Costs.

4.3 If the Landlord carries out major works of repair maintenance and decoration or replaces major items of plant or machinery it may:

(a) apportion the relevant expenditure over more than one Service Charge Period and

(b) include in the Landlord’s Costs interest at a commercially competitive rate on the part of the expenditure to be recovered in later Service Charge Periods.

5 **LANDLORD'S PROTECTION PROVISIONS**

5.1 The Tenant may not object to the Landlord's Costs or otherwise on any of the following grounds:

(a) the inclusion in a subsequent Service Charge Period of any item of expenditure or liability omitted from the Landlord's Costs for any earlier Service Charge Period so long as the Landlord has acted in good faith;

(b) an item of Landlord's Costs included at a proper cost might have been provided or performed at a lower cost;

(c) disagreement with any estimate of future expenditure for which the Landlord requires to make provision so long as the Landlord has acted reasonably and in good faith and in the absence of manifest error;

(d) the manner in which the Landlord exercises its discretion in providing Services so long as the Landlord acts in good faith and in accordance with the principles of good estate management;

(e) the employment of a Group Company to carry out and provide on the Landlord's behalf any of the Services;

(f) the employment of managing agents to carrying out and provide on the Landlord's behalf any of the Services; or

(g) the benefit of a service provided by the Landlord will be enjoyed substantially at a time after the expiry of the Lease if the service is provided by the Landlord in good faith and it is generally of benefit to the tenants and occupiers of the Building as a class.

5.2 This Schedule does not impose on the Landlord any obligation to make good damage caused by an Insured Risk.

6 **VACANT PARTS OF THE BUILDING AND ACTIONS BY THE LANDLORD**

6.1 The Service Charge will not be increased or altered because any Lettable Areas are vacant or occupied by the Landlord or any occupier of another part of the Building defaults in payment of his proportion of the Landlord's Costs.

6.2 Subject to paragraph 6.1 it is the intention that the Landlord should recover the whole of the Landlord's Costs from the Tenant and other occupiers of the Building.

6.3 If the Landlord recovers moneys in exercise of its powers referred to in paragraph 2.2(a) of Part 3 of this Schedule representing expenditure which has been or which would otherwise be included in the Landlord's Costs the Landlord will set off or credit them against the Landlord's Costs accordingly.

7 **MANAGEMENT CHARGES**

7.1 The Landlord will be entitled to include in the Landlord's Costs:

(a) a fee for the provision of Services (including the fees for employing managing agents and/or a Group Company for the carrying out and provision of Services but excluding any charge for rent collection); and

(b) any cost of the accountants, auditors or surveyors for auditing or certifying the Landlord's Costs or providing other similar services in connection with the Landlord's Costs.

7.2 In providing any of the Services the Landlord shall be entitled at its discretion to:

(a) employ agents contractors and such other persons as it may think fit; and

(b) delegate its duties and powers to them and their fees and expenses including any VAT payable shall form part of the Landlord's Costs.

8 **UNINSURED RISKS**

The Landlord shall only be entitled to include within the Service Charge any costs which the Landlord incurs in reinstating any damage or destruction caused by an Uninsured Risk to the Premises if:

(a) the Insured Risk shall have become an Uninsured Risk owing to the act or default of the Tenant or any person deriving title under the Tenant or their respective agents employees licensees or contractors; or

(b) such damage or destruction does not make the Building or the Premises or a substantial part of them unfit for occupation or use or inaccessible.

9 **TENANT PROTECTION PROVISIONS**

9.1 The following liabilities and expenses are to be excluded from the items comprising the Landlord's Costs:

(a) initial costs (including leasing of initial equipment) incurred in relation to the original design and construction of the Building (or redevelopment thereof prior to the date of this Lease) and the original plant and equipment serving or used in the Building;

(b) costs attributable to the initial establishment of services to the Building that are reasonably to be considered part of the original development or redevelopment costs of the Building prior to the date of this Lease;

(c) costs incurred in relation to the initial promotional launch of the Building;

(d) costs of administering applications for consent to assign sublet or alter by tenants or occupiers of the Building;

(e) costs for which the Tenant or other tenants or occupiers of the Building are individually responsible under the terms of their tenancy (or other arrangement by which they use or occupy the Building) and relate to matters they exclusively enjoy;

(f) costs arising from any damage or destruction to the Building caused by an Insured Risk;

(g) capital costs of the construction, redevelopment or extension of the Building;

(h) costs of upgrading, innovation or improvement resulting from any repair, maintenance, reinstatement, rebuilding or replacement that do not benefit the Tenant, but this will not prevent the Landlord from including costs within the Landlord's Costs where they arise:

(i) from advances in technology or quality or specification from that which was previously there;

(ii) where replacement or renewal is reasonable and cost-effective and will reduce operating costs for the benefit of the tenants of the Lettable Areas or improve the Environmental Rating of the Building;

(iii) from a requirement of the insurers or a requirement of any act of Parliament and any delegated law made under it;

(i) costs of any unlet Lettable Area;

(j) costs incurred in respect of the collection of rents;

(k) costs incurred in dealing with any lettings or rent reviews at the Building; and

(l) costs due from another tenant of the Building that are not recovered.

10 **THE LANDLORD'S OBLIGATION TO PROVIDE SERVICES**

10.1 Subject to the following provisions of this paragraph 10 the Landlord acting reasonably:

(a) will use reasonable endeavours to provide the Services itemised in Part 2 of this Schedule in an efficient manner; and

(b) may provide the Services itemised in Part 3 of this Schedule.

10.2 The Landlord will not be liable to the Tenant for failure to provide any Services:

(a) to the extent that the Landlord is prevented from doing so by Insured Risks, Uninsured Risks and other causes beyond the Landlord's reasonable control;

(b) unless the Landlord has had written notice of and a reasonable period in which to remedy the failure; or

(c) for any consequential economic or financial loss or damage or loss to property (save to the extent the Landlord has insured the loss) arising or resulting from or alleging to arise or result from any failure or alleged failure by the Landlord to perform the Services,

provided that the Landlord shall use reasonable endeavours to restore any services as soon as reasonably practicable.

10.3 The Landlord will not be liable to the Tenant for any loss damage or inconvenience which may be caused because of:

(a) temporary interruption of Services during periods of inspection maintenance repair and renewal or during the course of building works;

(b) the breakdown failure stoppage leaking bursting or defect of any Excluded Plant or of the Common Media or neighbouring property;

(c) any act, omission or negligence of any contractor, attendant or person undertaking the Services;

(d) any failure or delay in repair unless the Landlord has had notice of the same and reasonable time to investigate the matter and arrange for repair,

provided that the Landlord shall use reasonable endeavours to restore any services as soon as reasonably practicable and further provided that in any event, the Tenant will not be held liable to the Landlord for any loss or damage (including to the Premises) caused by any act, omission or negligence of any contractor, attendant or person engaged by the Landlord to undertake the Services.

10.4 The Landlord may vary extend alter or add (acting reasonably) to the Services in Part 3 of this Schedule if it considers that the interests of the occupiers of the Building as a class will be better served the amenities in the Building improved and/or the management of the Building more efficiently conducted.

10.5 The Landlord may not be required by the Tenant to provide the Services referred to in paragraphs 3 and 4 of Part 2 of this Schedule 7 outside normal office hours.

10.6 The Landlord will not be concerned in the administration and collection of or accounting for the Service Charge on an assignment of this Lease and accordingly the Landlord:

(a) will not be required to make any apportionment relative to the assignment; and

(b) may deal exclusively with the Tenant in whom this Lease is for the time being vested (and for this purpose in disregard of any assignment which has not been registered in accordance with Schedule 3 paragraph 24).

10.7 Where the Landlord (acting reasonably and having regard to the principles of good estate management) considers that it is prudent to pursue legal action against a third party having regard to the time and cost which this would be likely to involve when considered against the likelihood of recovery of damages or costs and the likely amount of damages or costs which would in the event of recovery be recovered, it shall use reasonable endeavours to enforce any claim, and take any proceedings against, any contractor, consultant, engineer, surveyor or any other professional or third party employed or engaged in connection with:

(a) the construction, refurbishment, and/or repair of the Common Parts; or

(b) the provision of the Services; or

(c) any service contract, warranty or guarantee relating to the Common Parts or the provision of the Services,

and credit any net sums which it receives (including any sums received in respect of the Premises) to the Service Charge account after having first deducted any proper costs and expenses incurred by or on behalf of the Landlord or other relevant party in pursuing such claim or proceedings to the extent not recovered as part of the service charge payable by tenants and other occupiers of the Building provided that any such action shall only be taken where:

(i) the cost of remedying the relevant defect has not or will not be recovered by the Landlord under any policy of insurance;

(ii) save where the Tenant has agreed to pay such costs, the costs of such enforcement or redress can properly be recovered through the Service Charge regime for the Building; and

(iii) the Landlord shall have obtained the Landlord's or other insurers' consent to any such action where the same is required under the relevant insurance policy.

Part 2

Mandatory Services and heads of charge

1 **COMMON PARTS**

1.1 Cleaning lighting and maintenance of the Common Parts.

1.2 Payment of any Outgoings in respect of the Common Parts.

1.3 Keeping the Common Parts clear of all rubbish.

1.4 Cleaning and clearing of Conducting Media.

1.5 Cleaning of all windows which do not form part of any Lettable Area and the external faces of all windows which although forming part of a Lettable Area give on to the Common Parts or form part of the exterior of the Building.

1.6 Operating a staffed reception desk in the entrance lobby of the Building during the Reception Hours.

2 **REPAIRS**

2.1 Repair decoration inspection maintenance renewal replacement resurfacing washing down cleaning and upkeep of the Main Structure including the Excluded Plant (without prejudice to the Tenant's responsibility for maintaining doors and windows) and the Common Parts, the Conducting Media, Common Media and other common service facilities and of plant equipment and tools and utensils serving or used in the Building.

2.2 Cleaning lighting repairing renewing replacing decorating maintaining and rebuilding any fences party walls party structures entrance ways stairs and passages and service areas and Conducting Media and any other items which are or may be used or enjoyed in common with neighbouring properties (whether the relevant costs and expenses are incurred by the Landlord or it is required to make a contribution to those incurred by the owners and occupiers of neighbouring properties or by a competent authority).

3 **HEATING AIR-CONDITIONING AND VENTILATION AND WATER**

3.1 Heating the Building as may be appropriate in the prevailing climatic conditions and air- conditioning and ventilation and providing hot water to the hot water taps in the Building.

3.2 Providing cold water to the cold water taps in the Building.

3.3 Repair, maintenance, inspection, renewal and replacement of all plant and equipment required for or in connection with the working and operation of heating air-conditioning and ventilation and hot and cold water.

4 **LIFTS**

4.1 Operation of a lift service in the Building.

4.2 Repair maintenance renewal and replacement of the lifts and of all plant and equipment for or in connection with the working and operation of the lifts.

5 **INSURANCES**

Engineering insurances for lifts boilers air conditioning plant lightning conductor equipment and all other electrical or mechanical equipment and apparatus in the Building save to the extent that the Tenant or any other tenant is responsible for effecting such insurance.

6 **STATUTORY REQUIREMENTS**

Compliance with the requirements of any statute or any government department local authority other public or competent authority or court of competent jurisdiction and of the insurers in relation to the use occupation and enjoyment of the Building which for the avoidance of doubt shall include the procurement of EPCs and any other form of energy or environmental certification required from time to time where such costs are not already paid for by a Tenant of a Lettable Area in accordance with the terms of this Lease.

Part 3

Non-mandatory Services and heads of charge

1 **ENERGY EFFICIENCY**

1.1 Carrying out any works to improve the Environmental Rating waste efficiency or water and waste water efficiency of the Common Parts.

1.2 Energy Costs in relation to the Common Parts or in relation to the provision of the Services.

2 **LEGAL PROCEDURES**

2.1 Making reasonable and proper representations against or contesting the provisions of any notice direction order certificate assessment or proposal affecting the whole or any part of the Building.

2.2 The proper costs of pursuing and enforcing any claim and taking or defending any proceedings:

(a) against any third party or parties employed in the construction refurbishment and/or repair of the Building or for the remedy of a defect or otherwise and

(b) to establish preserve or defend any rights amenities or facilities used or enjoyed by the occupiers of the Building or any part of it.

3 **EMPLOYEES**

3.1 Employment of a housekeeper facilities manager porter caretaker cleaning staff gardener or other staff for the maintenance and upkeep of and the provision of services and security in the Building including (without limitation upon the general operation of this paragraph) National Insurance and pension contributions of such employees.

3.2 Provision of uniforms overalls and protective clothing for such employees or other staff required in connection with their duties.

4 **COMMON PARTS**

4.1 Provision of and repair maintenance inspection renewal and replacement of directional and other informative notices in the Common Parts.

4.2 Furnishing carpeting equipping and ornamentation of the Common Parts.

4.3 Landscaping planting and replanting and the maintenance and upkeep of the Common Parts and of garden grassed areas and flagpoles on or within the Building.

5 **MANAGEMENT PREMISES**

5.1 Operating costs of Management Premises.

5.2 Payment of all Outgoings in respect of Management Premises.

5.3 Payment of any rent service charge or other costs payable by the Landlord or any deemed rents in relation to the Management Premises.

5.4 Provision maintenance inspection repair and replacement of equipment tools and utensils for the efficient management of the Services.

6 **REFUSE COLLECTION**

Provision of refuse and/or recycling facilities and refuse collection services.

7 **FIRE FIGHTING EQUIPMENT SECURITY AND PUBLIC ADDRESS**

7.1 Maintenance inspection repair and replacement of fire alarms and sprinkler systems.

7.2 Provision operation maintenance inspection repair and replacement of ancillary fire prevention apparatus fire fighting equipment telephone and public address systems and the closed circuit television and intruder alarm systems.

7.3 Security arrangements for the safety of occupiers and users of the Building and their property kept in the Building.

7.4 Engagement of security officers and security services.

8 **INSURANCES**

Such additional insurances (other than as referred to in paragraph 5 of Part 2 of this Schedule or in Schedule 6) as the Landlord reasonably effects in respect of or incidental to the Building its operation and management.

9 **AMENITIES IN COMMON PARTS**

Running in the Common Parts such amenities as the Landlord may reasonably determine are for the benefit of the occupiers of the Building.

10 **PEST CONTROL**

Provision of pest and infection control.

11 **OTHER CHARGES**

All other charges assessments and expenses (if any) reasonably incurred or paid by the Landlord or on its behalf in connection with the operation or maintenance or proper and convenient management of the Building.

12 **ENFORCING CLAIMS**

If required pursuant to paragraph 10.7 of Part 1 of Schedule 7, the proper costs of pursuing and enforcing any claim, and taking or defending any proceedings (such proper costs reasonably and fairly attributable to the Premises only) which the Landlord may in its discretion make, take or defend:

(a) against contractors, consultants, architects, consulting engineers and surveyors and any other professionals employed or engaged in connection with the construction and/or refurbishment and/or repair of the Building and/or the Premises or any other third party, for the remedy of a defect, repairs in or to the Building or otherwise for which they or any of them may be liable; and

(b) for the purpose of establishing, preserving or defencing any rights, amenities or facilities used or enjoyed by the tenants and occupiers of the Building or any part of it or to which they may be entitled.

SCHEDULE 8

Guarantee

Part 1

Covenants by the Guarantor

1. The Guarantor (if any) in consideration of the grant of this Lease (or the agreement to the assignment of this Lease as appropriate) covenants and guarantees with and to the Landlord that:

   (a) the Tenant will punctually pay the rents and perform and observe the covenants and other terms of this Lease;

   (b) if the Tenant defaults in so doing the Guarantor will pay the rents and perform or observe the covenants or terms in respect of which the Tenant is in default and on demand indemnify the Landlord against all liability arising or incurred by the Landlord as a result of default notwithstanding:

      (i) any time or indulgence granted by the Landlord to the Tenant or any neglect or forbearance of the Landlord in enforcing the payment of the rents or the observance or performance of the covenants or other terms of this Lease;

      (ii) that the terms of this Lease may have been varied by agreement between the parties (but subject to section 18 of the Landlord and Tenant (Covenants) Act 1995);

      (iii) that the Tenant has surrendered part of the Premises (when the liability of the Guarantor will continue in respect of the part not surrendered after making any necessary apportionments under section 140 of the Law of Property Act 1925);

      (iv) any refusal by the Landlord to accept payment of the Rent in order to avoid waiving a breach of the Tenant's covenants;

      (v) any Trigger Event;

      (vi) any other act or thing by which but for this provision the Guarantor would have been released;

      (vii) any legal limitations, immunity, disability, incapability or other circumstances relating to the Tenant, whether or not known to the Landlord; or

      (viii) the invalidity or unenforceability of any of the Tenant's covenants in this Lease or under any Authorised Guarantee Agreement.

2. It is hereby agreed that if any payment is made under the terms of this guarantee and the Guarantor is thereupon subrogated to all the Landlord's rights of recovery in relation thereto then the Guarantor shall not exercise any such rights against the Tenant.

3. This guarantee takes effect immediately on the grant (or the assignment as appropriate) of the lease to the Tenant and is to remain in force until the Tenant is released by law from liability under this Lease.

4. The Guarantor also covenants with the Landlord that if a Trigger Event occurs (where the Trigger Event is a Termination Trigger Event) the Landlord may within 12 months after the Trigger Event by notice (or where the Trigger Event is an Other Trigger Event at any time) require the Guarantor to accept a new lease of the Premises for a term equivalent to the residue which if there had been no disclaimer would have remained of the Term at the same rent and subject to the same terms as in this Lease immediately before the date of such

Trigger Event the new lease and the rights and liabilities under it to take effect from the date of such Trigger Event and the Guarantor will pay the costs incurred by the Landlord in connection with the new lease and the Guarantor will accept and complete the new lease. If there is more than one Guarantor, the Landlord may require one or more of them to accept a new lease.

5. If a Trigger Event occurs and the Landlord does not require the Guarantor to accept a new lease as above the Guarantor will pay to the Landlord on demand an amount equal to the difference between any money received by the Landlord for the use or occupation of the Premises less any expenditure incurred by the Landlord in connection with the Premises and the rents which would have been payable under the lease but for such Trigger Event in both cases for the period commencing with the date of such Trigger Event and ending on whichever is the earlier of the following dates:

   (a) where the Trigger Event was a Termination Trigger Event, six months from and including the Termination Trigger Event or, if earlier, the date on which the Landlord re-let the Premises; or

   (b) where the Trigger Event was an Other Trigger Event, when the Tenant is released from the covenants on the part of the Tenant pursuant to the Landlord and Tenant (Covenants) Act 1995.

Part 2

Exclusion of Sections 24-28 of the 1954 Act

1. The Landlord and the Guarantor agree to exclude the provisions of sections 24-28 (inclusive) of the 1954 Act in relation to the tenancy to be created by the new lease.

2. The Guarantor confirms that before it became contractually bound to enter into the new lease:

   (a) the Landlord served on the Guarantor a notice dated in relation to the tenancy created by the new lease (the "**Notice**") in a form complying with the requirements of Schedule 2 of the Order.

   (b) the Guarantor, or a person duly authorised by the Guarantor, in relation to the Notice made a statutory declaration (the "**Declaration**") dated in a form complying with the requirements of Schedule 2 of the Order.

3. The Guarantor confirms that, where the Declaration was made by a person other than the Guarantor, the declarant was duly authorised by the Guarantor to make the Declaration on Guarantor's behalf.

Part 3

Further Covenants by Guarantor

1. The Guarantor in consideration of the agreement to the assignment of this Lease covenants and guarantees with the Landlord that the Tenant will observe and perform its obligations under the Authorised Guarantee Agreement entered into by the Tenant pursuant to the terms of this Lease.

2. The Guarantor shall not:

   (a) seek to recover any sums from the Tenant; or

   (b) exercise any rights over the Tenant in respect of sums owed to the Guarantor; or

   (c) accept any money or other property from the Tenant,

   until the obligations guaranteed and indemnified pursuant to this Schedule have been discharged or performed in full.

3. The Guarantor shall not claim as a creditor in competition with the Landlord in relation to an Insolvency Event of the Tenant.

4. The Guarantor shall, at the request of the Landlord, join in any document that may be entered into by the Tenant in connection with this Lease or an Authorised Guarantee Agreement.

SCHEDULE 9

Category A Specification

EXECUTED as a **DEED** on behalf of	)	
NEW CONNECT INVESTMENTS LIMITED	)	
a company incorporated in	)	
BRITISH VIRGIN ISLANDS	)	/s/ Raymond Chun Wai Kwok
by Raymond Chun Wai Kwok	)	authorised signatory
	)	
and Connie Ngan Ying Lo	)	
	)	
being persons who, in accordance with	)	/s/ Connie Ngan Ying Lo
the laws of that territory, are acting	)	authorised signatory
under the authority of the company	)	
EXECUTED as a **DEED** by	)	
ORCHARD THERAPEUTICS LIMITED	)	
by a director in the presence of:	)	
	)	/s/ Mark Rothera, CEO
	)	Director
Witness Signature /s/ Gian Maria	)	
	)	
Witness Name: Gian Maria	)	
	)	
Witness Address 4 Thirlmererise	)	
Bromley	)	
BR1 4HY		