

14,285,715 American depositary shares Representing 14,285,715 ordinary shares



We are offering 14,285,715 American Depositary Shares, or ADSs. Each ADS represents one ordinary share. The ADSs may be evidenced by American Depositary Receipts, or ADRs. This is our initial public offering of our ADSs and no public market currently exists for our ADSs or ordinary shares.

The initial public offering price for our ADSs is \$14.00 per ADS. We have been approved to list our ADSs on The Nasdaq Global Select Market under the symbol "ORTX."

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

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

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

	Per ADS	Total
Public offering price	\$ 14.00	\$200,000,010
Underwriting discounts and commissions(1)	\$ 0.98	\$ 14,000,001
Proceeds to Orchard Therapeutics, before expenses	\$ 13.02	\$186,000,009

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

Delivery of the ADSs is expected to be made on or about November 2, 2018. We have granted the underwriters an option for a period of 30 days to purchase an additional 2,142,857 ADSs. If the underwriters exercise the option in full, the total underwriting discounts and commissions payable by us will be \$16.1 million, and the total proceeds available to us, before expenses, will be \$213.9 million.

At our request, the underwriters have reserved up to 714,285 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the initial public offering price per ADS through a directed share program to directors, officers, employees and certain other individuals associated with us. See "Underwriting."

J.P. Morgan

Goldman Sachs & Co. LLC
Wedbush PacGrow

Cowen

Prospectus dated October 30, 2018

Table of contents

	<u>Page</u>
Market, industry and other data	iii
About this prospectus	iv
Presentation of financial information	v
Prospectus summary	1
Risk factors	14
Special note regarding forward-looking statements	103
Exchange rate information	105
Use of proceeds	106
Dividend policy	107
Corporate reorganization	108
Capitalization	110
Dilution	112
Selected consolidated financial data	114
Management's discussion and analysis of financial condition and results of operations	117
Business	144
Management	205
Related party transactions	218
Principal shareholders	222
Description of share capital and articles of association	224
Description of American depositary shares	242
Shares and ADSs eligible for future sale	255
Material income tax considerations	257
Underwriting	267
Expenses of this offering	276
Legal matters	277
Experts	278
Service of process and enforcement of liabilities	279
Where you can find additional information	281
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.

[Table of Contents](#)

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

On October 29, 2018, we completed part of a corporate reorganization, as described under the section titled “Corporate reorganization,” pursuant to which Orchard Therapeutics Limited (now known as Orchard Therapeutics (Europe) Limited) became a wholly owned subsidiary of Orchard Therapeutics plc (formerly known as Orchard Rx Limited), a recently formed holding company with nominal assets and no liabilities, contingencies, or commitments, which has not conducted any operations prior to this offering other than acquiring the entire issued share capital of Orchard Therapeutics Limited. Orchard Rx Limited was re-registered as a public limited company and changed its name from Orchard Rx Limited to Orchard Therapeutics plc.

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. See “Corporate reorganization” for more information.

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

Presentation of financial information

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

We have made rounding adjustments to some of the figures included in this prospectus. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them. We have historically conducted our business through Orchard Therapeutics Limited and our U.S. subsidiary, and therefore our historical consolidated financial statements present the consolidated results of operations of Orchard Therapeutics Limited. Following the completion of our reorganization on October 29, 2018, our consolidated financial statements present the consolidated results of operations of Orchard Therapeutics plc.

Prospectus summary

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

Overview

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

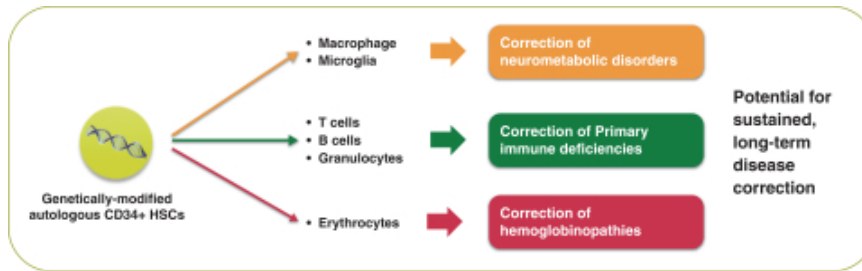
To date, our commercial product and clinical-stage product candidates have been administered in over 150 patients across five different diseases. These results, in combination with our deep expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide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

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

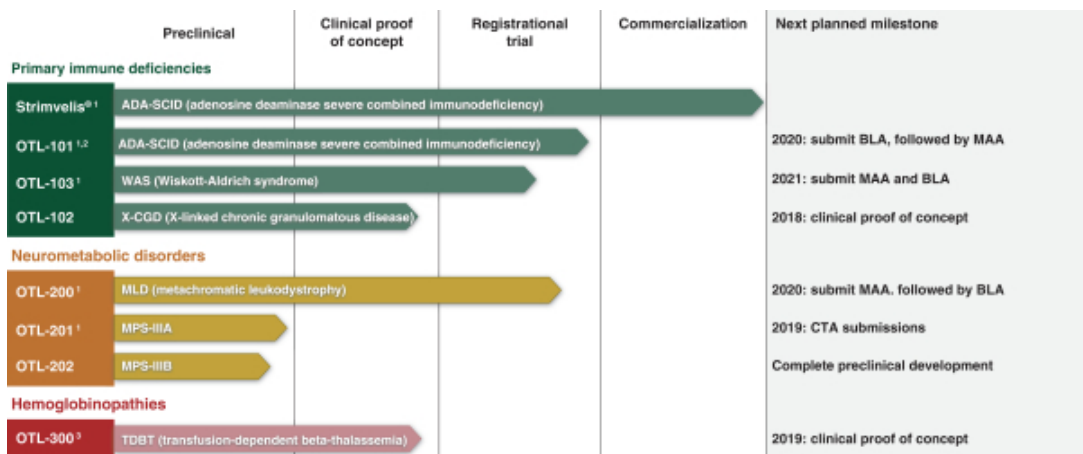
We intend to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. The indications we are initially targeting in our primary immune deficiencies and neurometabolic franchises (ADA-SCID, MLD, WAS, X-CGD, and MPS-III A) alone have a combined annual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

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

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



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



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

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

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

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

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

Our three lead product development programs are summarized below:

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

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

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

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

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

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

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

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

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

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

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

Corporate information

Orchard Therapeutics plc (formerly 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 corporate reorganization, all of the interests in Orchard Therapeutics Limited were exchanged for the same number and class of newly issued shares of Orchard Rx Limited

and, as a result, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited. On October 29, 2018, Orchard Rx Limited re-registered as a public limited company and changed its name to Orchard Therapeutics plc and Orchard Therapeutics Limited changed its name to Orchard Therapeutics (Europe) Limited. Please see “Corporate reorganization” for more information.

Recent financing

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

Risks associated with our business

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

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

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

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

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

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

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

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

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

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

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

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

The offering

ADSs offered by us	14,285,715 ADSs, each representing one ordinary share.
Underwriters' option to purchase additional ADSs	We have granted the underwriters an option for a period of 30 days from the date of this prospectus to purchase up to an additional 2,142,857 ADSs from us.
Ordinary shares to be outstanding immediately after this offering	84,047,200 ordinary shares (or 86,190,057 ordinary shares if the underwriters exercise in full their option to purchase an additional 2,142,857 ADSs).
American depositary shares	Each ADS represents one ordinary share, nominal value £0.10 per share. You will have the rights of an ADS holder or beneficial owner (as applicable) as provided in the deposit agreement among us, the depositary and holders and beneficial owners of ADSs from time to time. To better understand the terms of our ADSs, see "Description of American depositary shares." We also encourage you to read the deposit agreement, the form of which is filed as an exhibit to the registration statement of which this prospectus forms a part.
ADS depositary	Citibank, N.A.
Use of proceeds	We estimate that the net proceeds to us from this offering, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us, to be approximately \$181.9 million based on the initial public offering price of \$14.00 per ADS. We intend to use the net proceeds from this offering to fund ongoing development of our product candidates; ongoing commercialization of Strimvelis in the European Union and the expansion of our marketing and sales infrastructure in key markets, including the United States and Europe; design, construction, and operation of our own manufacturing facility; and the remainder for ongoing business development, general and administrative expenses, working capital and other general corporate purposes. See "Use of proceeds" for a more complete description of the intended use of proceeds from this offering.
Directed share program	At our request, the underwriters have reserved up to 714,285 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the initial public offering price per ADS through a directed share program,

to directors, officers, employees and certain other individuals associated with us. If purchased by these persons, these ADSs will not be subject to a lock-up restriction. The number of ADSs available for sale to the general public will be reduced by the number of reserved ADSs sold to these individuals. Any reserved ADSs not purchased by these individuals will be offered by the underwriters to the general public on the same basis as the other ADSs offered pursuant to this prospectus. See "Underwriting."

Risk factors

See "Risk factors" and the other information included in this prospectus for a discussion of factors you should carefully consider before deciding to invest in our ADSs.

Proposed Nasdaq Global Select Market listing "ORTX."

Unless otherwise stated in this prospectus, the 84,047,200 ordinary shares to be outstanding after this offering gives effect to the corporate reorganization described under the section titled "Corporate reorganization" and is based on 9,592,585 of our ordinary shares outstanding as of September 30, 2018, and gives effect to the conversion of all of our outstanding convertible preferred shares into 60,168,900 ordinary shares immediately prior to the closing of this offering, and excludes:

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

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

- the conversion of all of our outstanding convertible preferred shares into an aggregate of 60,168,900 ordinary shares upon the closing of this offering;
- no issuance or exercise of outstanding options after September 30, 2018;
- a 1-for-0.8003 reverse split of our ordinary and convertible preferred shares to be effected prior to the completion of this offering; and
- no exercise by the underwriters of their option to purchase up to 2,142,857 additional shares of ADSs in this offering.

Summary consolidated financial data

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

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

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

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

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

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

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

- (1) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the years ended December 31, 2016 and 2017, and for the six months ended June 30, 2017 and 2018, give effect to the 1-for-0.8003 reverse split of all ordinary shares that will be part of the corporate reorganization. Such pro forma data will become the historical net loss per share attributable to ordinary shares, basic and diluted, of Orchard Therapeutics plc upon consummation of the corporate reorganization.
- (2) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the periods ended December 31, 2017 and June 30, 2018 give effect to (i) the automatic conversion of all outstanding convertible preferred shares, as if the conversion had occurred at the later of January 1, 2017 or the issuance dates of the preferred shares, and (ii) the 1-for-0.8003 reverse split of all ordinary and convertible preferred shares; further, the shares to be sold in the proposed offering are excluded from the unaudited pro forma basic and diluted loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the year ended December 31, 2017 and the period ended June 30, 2018. See Note 10 to our audited financial statements included in this prospectus for further details on the calculation of unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders.
- (3) The pro forma balance sheet data gives effect to the sale of 13,942,474 (after giving effect to the 1-for-0.8003 reverse split) shares of Series C convertible preferred shares in August 2018 for net cash proceeds of \$148.0 million, which resulted in an increase of cash and additional paid-in capital of \$148.0 million. In addition, the pro forma balance sheet data gives effect to the conversion of all outstanding convertible preferred shares as of June 30, 2018 into an aggregate of 46,226,426 (after giving effect to the 1-for-0.8003 reverse split) ordinary shares upon the closing of this offering, which resulted in a reduction of convertible preferred shares of \$229.7 million and an increase in additional paid-in capital of \$229.7 million and \$1,000 of ordinary shares.
- (4) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 14,285,715 ADSs our ordinary shares in this offering at the initial public offering price of \$14.00 per ADS, after deducting underwriting discounts and commissions and estimated offering expenses payable by us. The pro forma as adjusted balance sheet also takes into account the corporate reorganization in which the nominal value of our ordinary shares is adjusted from £0.00001 to £0.08003 per share.
- (5) We define working capital as current assets less current liabilities.

Risk factors

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

Risks related to our financial position and need for additional capital

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

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

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

[Table of Contents](#)

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

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

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

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

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

Table of Contents

- 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,

[Table of Contents](#)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[Table of Contents](#)

- 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;

Table of Contents

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United

States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing such product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process.

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

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

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

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

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

change the standards for approval. Even if we obtain such designations for one or more of our product candidates, there can be no assurance that we will realize their intended benefits.

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

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a "rare pediatric disease" as a serious or life-threatening disease in which the serious or 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 recovered 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.

[Table of Contents](#)

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

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

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

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

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

criteria for orphan drug designation or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

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

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

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

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

regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

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

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

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

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

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

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

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in

emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

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

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

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

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

[Table of Contents](#)

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

[Table of Contents](#)

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

For example, bluebird bio is developing Lentiglobin, a lentiviral-based autologous *ex vivo* gene therapy for TDBT. In October 2018, bluebird bio announced that the EMA had accepted its MAA for Lentiglobin for the treatment of adolescents and adults with TDBT and a non- β^0/β^0 genotype. bluebird bio has publicly announced its intention to file a BLA in the United States for Lentiglobin in the future. This product candidate has been granted orphan drug status by both the FDA and EMA for the treatment of beta-thalassemia, Fast Track Designation by the FDA for the treatment of beta-thalassemia major, Breakthrough Therapy Designation by the FDA for the treatment of transfusion-dependent patients with beta-thalassemia major and Priority Medicines (PRIME) scheme by the EMA for the treatment of TDBT. If bluebird bio's product candidate receives marketing approval in the European Union or the United States, these designations may delay or prevent our ability to commercialize OTL-300 for TDBT for the applicable periods.

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

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

its gene editing approach for beta-thalassemia was approved in 2018. Several other approaches are under investigation to improve treatment outcomes in beta-thalassemia.

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

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

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

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

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

Because our internal research capabilities are limited, we may be dependent upon biotechnology companies, academic scientists and other researchers to sell or license product candidates,

approved products or the underlying technology to us. The success of this strategy depends partly upon our ability to identify, select, discover and acquire promising product candidates and products.

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

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

Risks related to manufacturing and supply

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

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

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

We have limited experience manufacturing our product candidates. We may be unable to produce clinical or commercial viral vectors or Strimvelis or our product candidates or meet

demand to support a clinical trial or a commercial launch for our product candidates. Any such failure could delay or prevent the development of our product candidates and would have a negative impact on our business, financial condition and results of operations.

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

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

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

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

The regulatory authorities may, at any time following approval of a product for sale, audit the manufacturing facilities for such product. If any such inspection or audit identifies a failure to

comply with applicable regulations, or if a violation of product specifications or applicable regulations occurs independent of such an inspection or audit, the relevant regulatory authority may require remedial measures that may be costly or time-consuming to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a manufacturing facility. Any such remedial measures imposed upon our CMOs or us could harm our business, financial condition, results of operations and prospects.

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

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

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

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

delays or prove costly. Even if we are successful, our manufacturing capabilities could be affected by cost-overruns, unexpected delays, equipment failures, labor shortages, natural disasters, power failures and numerous other factors that could prevent us from realizing the intended benefits of our manufacturing strategy and have a material adverse effect on our business.

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

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

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

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

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

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

Once collected from the patient, the cellular source material must be transported to the manufacturing facility using a shipping container that maintains the material at a cool temperature and be delivered typically within three days of collection. While we intend to use reputable couriers and agents for the transport of such materials, if the shipping container is opened or damaged such that the cool temperature is not maintained, the cellular source

material may be adversely impacted and it may not be feasible to manufacture a drug product for the patient. Similarly, if a shipment is delayed due to adverse weather, misrouting, other events or held up at a customs point, the cellular source material may not be delivered within a time window that will allow for its use for the successful manufacture of a drug product.

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

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

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

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

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

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

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

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

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

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

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

Risks related to our reliance on third parties

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

We have entered into licensing and collaboration agreements with third parties, including the GSK Agreement, pursuant to which GSK transferred to us Strimvelis, OTL-200 for MLD, OTL-103

[Table of Contents](#)

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;

[Table of Contents](#)

- 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

[Table of Contents](#)

reliance on our CMOs for certain manufacturing activities will reduce our control over these activities but will not relieve us of our responsibility to ensure compliance with all required regulations.

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

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

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

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

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

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

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

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

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

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

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

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing CMOs for our viral vectors and drug product, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials, including in some cases critical raw materials used in the manufacture thereof, must be manufactured in accordance with CGMP. Poor control of production processes can lead

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

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

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

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

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

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

[Table of Contents](#)

demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption in supply from any supplier or manufacturing location could lead to supply delays or interruptions which would damage our business, financial condition, results of operations and prospects.

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

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

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

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

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

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

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

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

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

Risks related to commercialization of our product candidates

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

If our product candidates are approved for commercialization, we currently intend to seek to commercialize them in the United States and Europe directly with specialized teams, given the relative rarity of the indications we are targeting. We currently have a limited marketing and sales team for the marketing, sales and distribution of our commercial product and our product

[Table of Contents](#)

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;

[Table of Contents](#)

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

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

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

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

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

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal

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

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

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

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

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

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign

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

The Tax Cuts and Jobs Act of 2017, or TCJA, includes a provision repealing, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise 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;

[Table of Contents](#)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

[Table of Contents](#)

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

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

[Table of Contents](#)

- 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

[Table of Contents](#)

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;

[Table of Contents](#)

- differing reimbursement regimes and price controls in certain non-U.S. markets;
- negative consequences from changes in tax laws;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad, including, for example, the variable tax treatment in different jurisdictions of options granted under our share option schemes or equity incentive plans;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- litigation or administrative actions resulting from claims against us by current or former employees or consultants individually or as part of class actions, including claims of wrongful terminations, discrimination, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

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

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

These developments, or the perception that any of them could occur, have had and may continue to have a significant adverse effect on global economic conditions and the stability of global financial markets, and could significantly reduce global market liquidity and restrict the ability of key market participants to operate in certain financial markets. In particular, it could also lead to a period of considerable uncertainty in relation to the U.K. financial and banking markets, as well as on the regulatory process in Europe. As a result of this uncertainty, global financial markets could experience significant volatility, which could adversely affect the market price of our ADSs. Asset valuations, currency exchange rates and credit ratings may also be subject to increased market volatility. Lack of clarity about future U.K. laws and regulations as the United Kingdom determines which European Union rules and regulations to replace or replicate in the event of a withdrawal, including financial laws and regulations, tax and free trade agreements, intellectual property rights, supply chain logistics, environmental, health and safety laws and

regulations, immigration laws and employment laws, could decrease foreign direct investment in the United Kingdom, increase costs, depress economic activity and restrict our access to capital. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms or if other EU Member States pursue withdrawal, barrier-free access between the United Kingdom and other EU Member States or among the EEA overall could be diminished or eliminated.

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

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

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

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

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

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

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

Risks related to our intellectual property

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

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

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

Parties making patent infringement claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to further develop and commercialize one or more of our products or product candidates. Defense of these claims, including demonstrating non-infringement, invalidity or unenforceability of the respective patent rights in question, regardless

of their merit, is time-consuming, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. For example, in order to successfully challenge the validity of any U.S. patent in federal court, we would need to overcome a presumption of validity. This is a high burden requiring us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, and we can provide no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. We may not have sufficient resources to bring these actions to a successful conclusion. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of our ADSs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we

regard as our own or such assignments may not be self-executing or may be breached. Our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

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

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

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

Competitors may infringe, misappropriate or otherwise violate patents, trademarks, copyrights or other intellectual property that we own or in-license. To counter infringement, misappropriation

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

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

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

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

[Table of Contents](#)

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;

Table of Contents

- 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 have been approved to have our ADSs listed on The Nasdaq Global Select 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;

[Table of Contents](#)

- additions or departures of key scientific or management personnel;
- significant lawsuits, including patent or shareholder litigation;
- changes in the market valuations of similar companies;
- sales of our ADSs by us or our shareholders in the future; and
- the trading volume of our ADSs.

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

We could be subject to securities class action litigation.

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

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

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

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

Our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 61.6% of our ordinary shares and, upon closing of this offering, that same group will beneficially own approximately 50.9% of our outstanding ordinary shares. Depending on the level of attendance at our general meetings of shareholders, these shareholders either alone or voting together as a group may be in a position to determine or significantly influence the outcome of decisions taken at any such general meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our general meetings of shareholders may control any shareholder resolution requiring a simple majority, including the appointment of board members, certain decisions relating to our capital structure, the approval of certain significant corporate transactions and amendments to

our Articles of Association. Among other consequences, this concentration of ownership may prevent or discourage unsolicited acquisition proposals that you may believe are in your best interest as one of our shareholders. Some of these persons or entities may have interests different than yours. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs are being sold in this offering and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

If our existing shareholders sell, or indicate an intent to sell, substantial amounts of our securities in the public market, the trading price of the ADSs could decline significantly and could decline below the public offering price in this offering. Upon completion of this offering, and assuming no exercise of the underwriters' option to purchase additional ADSs, we will have 84,047,200 outstanding ordinary shares (including ordinary shares represented by the ADSs), of which approximately 69,761,485 are subject to a 180-day contractual lock-up. The representatives of the underwriters may permit us and the holders of the lock-up shares to sell shares or ADSs prior to the expiration of the lock-up agreements. See "Underwriting." After the lock-up agreements pertaining to this offering expire, and based on the number of ordinary shares (including ordinary shares represented by ADSs) outstanding upon completion of this offering, these approximately 69,761,485 additional ordinary shares will be eligible for sale in the public market, all of which shares are held by directors and certain members of our executive management and will be subject to volume limitations under Rule 144 under the Securities Act of 1933, as amended, or the Securities Act, for sales in the United States. In addition, ordinary shares subject to outstanding options under our equity incentive plans and the ordinary shares reserved for future issuance under our equity incentive plan will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. We also intend to enter into a registration rights agreement upon the closing of this offering pursuant to which we will agree under certain circumstances to file a registration statement to register the resale of the ordinary shares held by certain of our existing shareholders, as well as to cooperate in certain public offerings of such ordinary shares. In addition, we intend to register all ordinary shares that we may issue under our equity compensation plans. Once we register these ordinary shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Shares and ADSs eligible for future sale" section of this prospectus.

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

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

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

ADSs are transferable on the books of the depository. However, the depository 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 depository may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depository are closed, or at any time if we or the depository 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 depository 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 depository shares."

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

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

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

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

[Table of Contents](#)

If this jury trial waiver provision is not permitted by applicable law, an action could proceed under the terms of the deposit agreement with a jury trial. If we or the depository opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the United States Supreme Court. However, we believe that a contractual pre-dispute jury trial waiver provision is generally enforceable, including under the laws of the State of New York, which govern the deposit agreement, by a federal or state court in the City of New York, which has non-exclusive jurisdiction over matters arising under the deposit agreement. In determining whether to enforce a contractual pre-dispute jury trial waiver provision, courts will generally consider whether a party knowingly, intelligently and voluntarily waived the right to a jury trial. We believe that this is the case with respect to the deposit agreement and the ADSs. It is advisable that you consult legal counsel regarding the jury waiver provision before entering into the deposit agreement.

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

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

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

Except as described in this prospectus and the deposit agreement, holders of the ADSs will not be able to exercise voting rights attaching to the ordinary shares represented by the ADSs. Under the terms of the deposit agreement, holders of the ADSs may instruct the depository 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 depository, 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 depository 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 depository 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

[Table of Contents](#)

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 \$9.90 per ADS, based on the initial public offering price of \$14.00 per ADS, after deducting underwriting discounts and commissions and estimated offering expenses payable by us, and our pro forma as adjusted net tangible book value as of June 30, 2018. Further, investors purchasing ADSs in this offering will contribute approximately 41.2% of the total amount invested by shareholders since our inception, but will own only approximately 17.0% of the ordinary shares outstanding. For information on how the foregoing amounts were calculated, see "Dilution."

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

Sales of a substantial number of our ADSs in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. After this offering, assuming no exercise of the underwriters' option to purchase additional ADSs, we will have outstanding 84,047,200 ordinary shares based on the number of ordinary shares outstanding as of September 30, 2018, (or 86,190,057 ordinary shares if the underwriters exercise their option to purchase additional ADSs in full). This includes the 14,285,715 ADSs that we are selling in this offering (or 16,428,572 ADSs if the underwriters exercise their option to purchase additional ADSs in full), which may be resold in the public market immediately without restriction, unless purchased by our affiliates. The remaining 69,761,485 shares currently are restricted as a result of securities laws or lock-up agreements but will be able to be sold after the offering as described in the "Shares and ADSs eligible for future sale" and "Underwriting" sections of this prospectus. Moreover, after this offering, holders of an aggregate of approximately 60,168,900 ordinary shares will have rights, subject to certain conditions, to require us to file registration statements covering their ordinary shares or to include their ordinary shares in registration statements that we may file for ourselves or other shareholders. In addition, 10,135,454 ordinary shares reserved for issuance upon the exercise of existing options outstanding as of September 30, 2018 under our current equity incentive plan will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations. We intend to register all ordinary shares that we may issue under our equity compensation plans. Once we register these ordinary shares, they can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and the lock-up agreements described in the "Underwriting" section of this prospectus.

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

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

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

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

We are incorporated under English law. Certain members of our board of directors and senior management are non-residents of the United States, and all or a substantial portion of our assets

and the assets of such persons are located outside the United States. As a result, it may not be possible to serve process on such persons or us in the United States or to enforce judgments obtained in U.S. courts against them or us based on civil liability provisions of the securities laws of the United States. As a result, it may not be possible for investors to effect service of process within the United States upon such persons or to enforce judgments obtained in U.S. courts against them or us, including judgments predicated upon the civil liability provisions of the U.S. federal securities laws.

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

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

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

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

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

protections or information generally available to investors holding shares in public companies organized in the United States.

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

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

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

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

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

As a foreign private issuer, we are not required to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers. We may no longer be a foreign private issuer as early as June 30, 2019 (the end of our second fiscal quarter in the fiscal year after completion of this offering), which would require us to comply with all of the periodic disclosure and current reporting requirements of the Exchange Act applicable to U.S. domestic issuers as of January 1, 2020. In order to maintain our current status as a foreign private issuer, either (a) a majority of our securities must be either directly or indirectly owned of record by non-residents of the United States or (b)(i) a majority of our executive officers or directors cannot be U.S. citizens or residents, (ii) more than 50% of our assets must be located outside the United States and (iii) our business must be administered principally outside the United States. If we lose our status as a foreign private issuer, we would be required to comply with the Exchange Act reporting and other requirements applicable to U.S. domestic issuers, which are more detailed and extensive than the requirements for foreign private issuers. We may also be required to make changes in our corporate governance practices in accordance with various SEC and Nasdaq rules. The regulatory and compliance costs to us under U.S. securities laws if we are required to comply with the reporting requirements applicable to a U.S. domestic issuer may be significantly higher than the cost we would incur as a

foreign private issuer. As a result, we expect that a loss of foreign private issuer status would increase our legal and financial compliance costs and is likely to make some activities highly time consuming and costly. We also expect that if we were required to comply with the rules and regulations applicable to U.S. domestic issuers, it would make it more difficult and expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced coverage or incur substantially higher costs to obtain coverage. These rules and regulations could also make it more difficult for us to attract and retain qualified members of our board of directors.

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

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

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

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

In addition, the JOBS Act provides that an EGC may take advantage of an extended transition period for complying with new or revised accounting standards. This allows an EGC to delay the

adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

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

As a U.S. public company, and particularly after we are no longer an EGC, we will incur significant legal, accounting and other expenses that we did not incur as a private company. In addition, the Sarbanes-Oxley Act and rules subsequently implemented by the SEC and Nasdaq have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will make some activities more time-consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance.

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

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

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

improvement. Inferior internal controls could also cause investors to lose confidence in our reported financial information, which could have a negative effect on the trading price of our ADSs.

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

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

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

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

We expect to incur additional costs to remediate these control deficiencies, though there can be no assurance that our efforts will be successful or avoid potential future material weaknesses. If we are unable to successfully remediate our existing or any future material weaknesses in our internal control over financial reporting, or if we identify any additional material weaknesses, the accuracy and timing of our financial reporting may be adversely affected, we may be unable to maintain compliance with securities law requirements regarding timely filing of periodic reports in addition to applicable stock exchange listing requirements, investors may lose

confidence in our financial reporting, and our ADS price may decline as a result. We also could become subject to investigations by Nasdaq, the SEC or other regulatory authorities.

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

Upon completion of this offering, we will become subject to certain reporting requirements of the Exchange Act. Our disclosure controls and procedures are designed to reasonably assure that information required to be disclosed by us in reports we file or submit under the Exchange Act is accumulated and communicated to management, recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements or insufficient disclosures due to error or fraud may occur and not be detected.

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

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

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

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

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

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

Under the Code, we will be a PFIC, for any taxable year in which (1) 75% or more of our gross income consists of passive income or (2) 50% or more of the average quarterly value of our assets consists of assets that produce, or are held for the production of, passive income. For purposes of these tests, passive income includes dividends, interest, gains from the sale or exchange of investment property and certain rents and royalties. In addition, for purposes of the above calculations, a non-U.S. corporation that directly or indirectly owns at least 25% by value of the shares of another corporation is treated as holding and receiving directly its proportionate share of assets and income of such corporation. If we are a PFIC for any taxable year during which a U.S. Holder holds our shares, the U.S. Holder may be subject to adverse tax consequences regardless of whether we continue to qualify as a PFIC, including ineligibility for any preferred tax rates on capital gains or on actual or deemed dividends, interest charges on certain taxes treated as deferred and additional reporting requirements.

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

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

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

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

As a U.K. incorporated and tax resident entity, we are subject to U.K. corporate taxation on tax-adjusted trading profits. Due to the nature of our business, we have generated losses since inception and therefore have not paid any U.K. corporation tax. As of December 31, 2017, we had cumulative carryforward tax losses of \$48.4 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to U.K. profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus an incremental 50% of U.K. taxable profits. In addition, if we were to have a major change in the nature of the conduct of our trade, loss carryforwards may be restricted or extinguished.

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

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

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

In connection with the Corporate Reorganization, the entire issued share capital of Orchard Therapeutics Limited was transferred to the Company. The Company will make an application to HM Revenue & Customs for such transfer to be adjudicated as not chargeable to stamp duty by virtue of section 77 of the Finance Act 1986. While it is expected that all of the conditions of section

77 of the Finance Act 1986 can be satisfied and relief should be available, if such relief is not forthcoming the Company will be required to pay 0.5% stamp duty of the value of the consideration given for that transfer, which is expected to be, broadly, 0.5% of the value of the Orchard Therapeutics Limited share capital transferred.

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

On October 29, 2018, we re-registered as a public limited company incorporated in England and Wales. Our place of central management and control is currently in the United Kingdom. Accordingly, we are currently subject to the Takeover Code and, as a result, our shareholders are entitled to the benefit of certain takeover offer protections provided under the Takeover Code. The Takeover Code provides a framework within which takeovers of companies are regulated and conducted. If, at the time of a takeover offer, the Panel on Takeovers and Mergers determines that we do not have our place of central management and control in the United Kingdom, then the Takeover Code would not apply to us and our shareholders would not be entitled to the benefit of the various protections that the Takeover Code affords. In particular, we would not be subject to the rules regarding mandatory takeover bids. The following is a brief summary of some of the most important rules of the Takeover Code:

- When a person or group (a) acquires interests in shares carrying 30% or more of the voting rights of a company (which percentage is treated by the Takeover Code as the level at which effective control is obtained) or (b) increases the aggregate percentage interest they have when they are already interested in not less than 30% and not more than 50%, they must make a cash offer to all other shareholders at the highest price paid by them in the 12 months before the offer was announced.
- When interests in shares carrying 10% or more of the voting rights of a class have been acquired by an offeror (i.e., a bidder) in the offer period (i.e. before the shares subject to the offer have been acquired) and the previous 12 months, the offer must include a cash alternative for all shareholders of that class at the highest price paid by the offeror in that period. Further, if an offeror acquires for cash any interest in shares during the offer period, a cash alternative must be made available at a price at least equal to the price paid for such shares.
- If the offeror acquires an interest in shares in an offeree company (i.e., a target) at a price higher than the value of the offer, the offer must be increased accordingly.
- The offeree company must appoint a competent independent adviser whose advice on the financial terms of the offer must be made known to all the shareholders, together with the opinion of the board of directors of the offeree company.
- Favorable deals for selected shareholders are not permitted, except in certain circumstances where independent shareholder approval is given and the arrangements are regarded as fair and reasonable in the opinion of the financial adviser to the offeree.
- All shareholders must be given the same information.
- Those issuing takeover circulars must include statements taking responsibility for the contents thereof.
- Profit forecasts, quantified financial benefits statements and asset valuations must be made to specified standards and must be reported on by professional advisers.

[Table of Contents](#)

- Misleading, inaccurate or unsubstantiated statements made in documents or to the media must be publicly corrected immediately.
- Actions during the course of an offer by the offeree company, which might frustrate the offer are generally prohibited unless shareholders approve these plans. Frustrating actions would include, for example, lengthening the notice period for directors under their service contract or agreeing to sell off material parts of the target group.
- Stringent requirements are laid down for the disclosure of dealings in relevant securities during an offer, including the prompt disclosure of positions and dealing in relevant securities by the parties to an offer and any person who is interested (directly or indirectly) in 1% or more of any class of relevant securities.
- Employees of both the offeror and the offeree company and the trustees of the offeree company's pension scheme must be informed about an offer. In addition, the offeree company's employee representatives and pension scheme trustees have the right to have a separate opinion on the effects of the offer on employment appended to the offeree board of directors' circular or published on a website.

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

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

The principal differences include the following:

- Under English law and our Articles of Association, each shareholder present at a meeting has only one vote unless demand is made for a vote on a poll, in which case each holder gets one vote per share owned. Under U.S. law, each shareholder typically is entitled to one vote per share at all meetings.
- Under English law, it is only on a poll that the number of shares determines the number of votes a holder may cast. You should be aware, however, that the voting rights of ADSs are also governed by the provisions of a deposit agreement with our depository bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of Association. This may make it more difficult for us to complete

[Table of Contents](#)

corporate transactions deemed advisable by our board of directors. Under U.S. law, generally only majority shareholder approval is required to amend the certificate of incorporation or to approve other significant transactions.

- In the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, for so long as we continue to be subject to the UK Takeover Code, a bidder seeking to acquire us by means of a takeover offer would need to make an offer for all of our outstanding ordinary shares/ADSs. If acceptances are not received for 90% or more of the ordinary shares/ADSs under the offer, under English law, the bidder cannot complete a “squeeze out” to obtain 100% control of us. Accordingly, acceptances of 90% of our outstanding ordinary shares/ADSs will likely be a condition in any takeover offer to acquire us, not 50% as is more common in tender offers for corporations organized under Delaware law. By contrast, a scheme of arrangement, the successful completion of which would result in a bidder obtaining 100% control of us, requires the approval of a majority of shareholders voting at the meeting and representing 75% of the ordinary shares voting for approval.
- Under English law and our Articles of Association, shareholders and other persons whom we know or have reasonable cause to believe are, or have been, interested in our shares may be required to disclose information regarding their interests in our shares upon our request, and the failure to provide the required information could result in the loss or restriction of rights attaching to the shares, including prohibitions on certain transfers of the shares, withholding of dividends and loss of voting rights. Comparable provisions generally do not exist under U.S. law.
- The quorum requirement for a shareholders’ meeting is a minimum of two shareholders entitled to vote at the meeting and present in person or by proxy or, in the case of a shareholder which is a corporation, represented by a duly authorized officer. Under U.S. law, a majority of the shares eligible to vote must generally be present (in person or by proxy) at a shareholders’ meeting in order to constitute a quorum. The minimum number of shares required for a quorum can be reduced pursuant to a provision in a company’s certificate of incorporation or bylaws, but typically not below one-third of the shares entitled to vote at the meeting.

Special note regarding forward-looking statements

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

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

[Table of Contents](#)

- 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) (\$ per £1.00)	Low	High
2013	1.6574	1.5642	1.4837	1.6574
2014	1.5578	1.6484	1.5517	1.7165
2015	1.4746	1.5284	1.4648	1.5882
2016	1.2337	1.3555	1.2155	1.4800
2017	1.3529	1.2890	1.2118	1.3578
2018 (through October 12, 2018)	1.3154	1.3499	1.2685	1.4332

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

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

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

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

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

Use of proceeds

We estimate that the net proceeds to us in this offering will be \$181.9 million, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, based on the initial public offering price of \$14.00 per ADS. If the underwriters exercise their option to purchase additional ADSs in full, we estimate that the net proceeds to us from this offering will be \$209.8 million, after deducting the estimated underwriting discounts and commissions and estimated offering expenses payable by us.

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

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

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

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

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

Dividend policy

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

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

Corporate reorganization

Pursuant to a corporate reorganization, all shareholders of Orchard Therapeutics Limited exchanged 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 became a wholly owned subsidiary of Orchard Rx Limited. Subsequently, on October 29, 2018 Orchard Rx Limited re-registered as a public limited company and changed its name to Orchard Therapeutics plc. Prior to the re-registration of Orchard Rx Limited as a public company, Orchard Therapeutics Limited changed 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 acquired 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 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.

Exchange of Orchard Therapeutics Limited shares for Orchard Rx Limited shares

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

Reduction of Capital of Orchard Rx Limited

Following the share exchange, on October 26, 2018, Orchard Rx Limited reduced its issued share capital pursuant to Part 17 of the Companies Act 2006 by reducing the nominal value of each issued share from £7.00 to £0.08003. The amount of the reduction of share capital will be credited to Orchard Rx Limited’s reserves available for distribution.

Re-registration of Orchard Rx Limited as Orchard Therapeutics plc

Following the steps described above, on October 29, 2018, Orchard Rx Limited re-registered as a public limited company and changed its name to Orchard Therapeutics plc. Such re-registration required the passing of special resolutions by the current shareholders of Orchard Rx Limited to approve the re-registration as a public limited company, the name change to Orchard Therapeutics plc and the adoption of a new articles of association for Orchard Therapeutics plc. Prior to the re-registration of Orchard Rx Limited as a public limited company, Orchard Therapeutics Limited changed its name to Orchard Therapeutics (Europe) Limited.

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

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

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

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

Certain further resolutions have been passed by the shareholders in connection with this offering, details of which are set out in the section titled "Description of share capital and articles of association."

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

Capitalization

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

- an actual basis, not reflecting the 1-for-0.8003 reverse share split to be effected prior to completion of this offering; and
- a pro forma basis to give effect to:
 - our sale of 13,942,474 shares of Series C convertible preferred shares in August 2018 at a price of \$10.76 per share for net proceeds of \$148.0 million and conversion into an aggregate of 13,942,474 ordinary shares upon closing of this offering which resulted in an increase of cash and additional paid-in capital of \$148.0 million;
 - a 1-for-0.8003 reverse share split to be effected prior to completion of this offering;
 - the conversion of all outstanding convertible preferred shares as of June 30, 2018 into an aggregate of 46,226,426 ordinary shares upon the closing of this offering which resulted in a reduction of convertible preferred shares of \$229.7 million and increase of ordinary shares of \$1,000 and additional paid-in capital of \$229.7 million; and
- on a pro forma as adjusted basis giving effect to the pro forma adjustments set forth above and to give further effect to the sale of 14,285,715 ADSs in this offering at the initial public offering price of \$14.00 per ADS, after deducting estimated underwriting discounts and commissions and estimated offering expenses payable by us.

[Table of Contents](#)

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

	As of June 30, 2018 (in thousands, except share and per share data)		
	Actual (as restated)	Pro forma	Pro forma as adjusted ⁽¹⁾
Cash	\$ 48,762	\$ 196,742	\$ 378,592
Shareholders' equity:			
Convertible preferred shares, £0.00001 par value; 46,226,426 shares authorized, 46,226,426 shares issued and outstanding as of June 30, 2018; no shares authorized, issued and outstanding, pro forma; no shares authorized, issued and outstanding, pro forma as adjusted	229,709	—	—
Ordinary shares, £0.00001 par value; 11,793,356 shares issued and outstanding, actual; 69,761,485 shares issued and outstanding, pro forma; 84,047,200 shares issued and outstanding, pro forma as adjusted	—	1	8,780
Additional paid-in capital	9,885	387,572	560,643
Accumulated other comprehensive (loss) income	6,097	6,097	6,097
Accumulated deficit	(230,945)	(230,945)	(230,945)
Total shareholders' equity	14,746	162,725	344,575
Total capitalization	\$ 14,746	\$ 162,725	\$ 344,575

(1) The pro forma as adjusted balance sheet data give further effect to our issuance and sale of 14,285,715 shares of our ordinary shares in this offering at the initial public offering price of \$14.00 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

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

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

Dilution

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

After giving effect to (i) the issuances of ordinary shares since June 30, 2018 and our Series C issuances in August 2018, (ii) our corporate reorganization (including a 1-for-0.8003 reverse stock split) and (iii) the sale of 14,285,715 ADSs in this offering at the initial public offering price of \$14.00 per ADS, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our pro forma as adjusted net tangible book value at June 30, 2018 would have been \$4.10 per ordinary share, or \$4.10 per ADS. This represents an immediate increase in pro forma as adjusted net tangible book value, after considering all issuances subsequent to June 30, 2018, of \$1.77 per ADS to new investors and immediate dilution of \$9.90 per ADS to new investors. The following table illustrates this dilution to new investors purchasing ADSs in this offering:

Initial public offering price per ADS		\$14.00
Historical net tangible book value per ADS as of June 30, 2018	\$ 1.56	
Effect of ordinary share issuances since June 30, 2018(1)	(0.02)	
Effect attributable to issuance of Series C and conversion to ordinary shares(2)	5.37	
Effect attributable to our corporate re-organization(3)	(4.58)	
Pro forma net tangible book value per share as of June 30, 2018 before new investors purchasing ADSs in this offering	2.33	
Effect attributable to new investors purchasing ADSs in this offering(4)	1.77	
Pro forma as adjusted net tangible book value per ADS as of June 30, 2018		4.10
Dilution per share to new investors purchasing ADSs in this offering		\$ 9.90

- (1) 154,369 outstanding ordinary shares were included in this calculation to give effect to the issuance of ordinary shares subsequent to June 30, 2018.
- (2) 13,924,474 outstanding ordinary shares were included in this calculation to give effect to the sale of our Series C convertible preferred shares for net cash proceeds of \$148.0 million in August 2018 and subsequent conversion of these shares into ordinary shares.
- (3) 69,761,485 outstanding ordinary shares were included in the dilution per share calculation attributable to the corporate reorganization, (including the Series C convertible preferred shares).
- (4) 84,047,200 outstanding ordinary shares were included in the dilution per share calculation attributable to new investors purchasing ADSs in this offering.

If the underwriters exercise their option to purchase additional ADSs in full, the pro forma as adjusted net tangible book value per ADS after the offering would be \$4.32, the increase in net tangible book value per ADS to existing shareholders would be \$1.99 and the immediate dilution in net tangible book value per ADS to new investors in this offering would be \$9.68.

The following table summarizes, on the pro forma as adjusted basis described above as of June 30, 2018, the differences between the existing shareholders and the new investors in this

[Table of Contents](#)

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 the initial public offering price of \$14.00 per ADS, before deducting underwriting discounts and commissions and estimated offering expenses payable by us.

	Ordinary shares/ ADSs purchased		Total consideration		Average price per ordinary shares/ADS
	Number	Percent	Amount	Percent	
Existing shareholders	69,761,485	83.0%	\$ 285,603,621	58.8%	\$ 4.09
New investors participating in this offering	14,285,315	17.0%	200,000,010	41.2%	\$ 14.00
Total	84,047,200	100.0%	\$485,603,631	100.0%	

If the underwriters exercise their option to purchase additional ADSs in full, the percentage of ordinary shares held by existing shareholders will decrease to 80.9% of the total number of ordinary shares outstanding after the offering, and the number of shares held by new investors will be increased to 16,428,572, or 19.1% 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 became effective upon the signing of the underwriting agreement related to this offering, as well as any automatic increases in the number of ordinary shares reserved for issuance under the 2018 Plan and any contingent issuances under existing agreements providing for the issuance of shares based on achievement of performance milestones.

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

Selected consolidated financial data

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

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

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

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

[Table of Contents](#)

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

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

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

- (1) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the years ended December 31, 2016 and 2017, and for the six months ended June 30, 2017 and 2018, give effect to the 1-for-0.8003 reverse split of all ordinary shares that will be part of the corporate reorganization. Such pro forma data will become the historical net loss per share attributable to ordinary shares, basic and diluted, of Orchard Therapeutics plc upon consummation of the corporate reorganization.
- (2) As described in Note 2 to our audited financial statements included in this prospectus, the unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the periods ended December 31, 2017 and June 30, 2018 give effect to (i) the automatic conversion of all outstanding convertible preferred shares, as if the conversion had occurred at the later of January 1, 2017 or the issuance dates of the preferred shares, and (ii) the 1-for-0.8003 reverse split of all ordinary and convertible preferred shares; further, the shares to be sold in the proposed offering are excluded from the unaudited pro forma basic and diluted loss per share to ordinary shareholders and unaudited pro forma weighted-average number of basic and diluted ordinary shares for the year ended December 31, 2017 and the period ended June 30, 2018. See Note 10 to our audited financial statements included in this prospectus for further details on the calculation of unaudited supplemental pro forma basic and diluted net loss per share to ordinary shareholders.
- (3) We define working capital as current assets less current liabilities.

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

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

Overview

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

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

We are initially focusing our autologous ex vivo gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Our portfolio currently includes Strimvelis, our commercial-stage gammaretroviral-based product for the treatment of ADA-SCID, five lentiviral product candidates in clinical-stage development and several other product candidates in preclinical development. We expect to submit a BLA with the FDA for our product candidate OTL-101, a lentiviral gene therapy for ADA-SCID, in 2020, followed by an MAA with the EMA. We also plan to submit an MAA with the EMA for our next most advanced clinical candidate, OTL-200 for the treatment of MLD, in 2020 followed by a BLA with the FDA.

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

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

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

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

Recent developments

Our agreement with GSK

In April 2018, we entered into the GSK Agreement, with GSK, pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS, and OTL-300, a clinical-stage gene therapy program for TDBT, and in connection with which we acquired non-exclusive rights to certain third-party intellectual property, including rights related to lentiviral vector technology to develop and commercialize OTL-200 for MLD and OTL-103 for WAS. In addition, GSK novated to us their R&D Agreement with Telethon-OSR, which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Milan, Italy for MPS-I, CGD and GLD.

Under the GSK Agreement, we are required to use our best endeavors to continue to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in the European Union, and at all times at the San Raffaele Hospital in Milan, Italy provided that a minimum number of patients continue to be treated at this site. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement. In addition, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we are required to first use best endeavors to file an MAA for

OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and submit an MAA or BLA, as applicable, for OTL-300 for TDBT in either the United States or Europe.

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

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

Our agreement with Telethon-OSR

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

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

Issuance of Series C convertible preferred shares

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

Components of our results of operations

Revenue

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

Operating expenses

Research and development expenses

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

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

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

We expense research and development cost as incurred. We recognize external development costs based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as a prepaid expense or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. See "—Income tax (expense) benefit."

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

[Table of Contents](#)

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

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

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

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

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related regulatory compliance for Strimvelis in the European Union;

[Table of Contents](#)

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

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

General and administrative expenses

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

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

Other income (expense), net

Interest income

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

Change in fair value of tranche obligations

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

Other income (expense)

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

Income tax (expense) benefit

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

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

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

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

[Table of Contents](#)

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

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

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

Results of operations

Comparison of the years ended December 31, 2016 and 2017

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

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

[Table of Contents](#)

Research and development expenses

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

	Year ended December 31,		Change
	2016	2017	
	(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-III A	3,565	3,158	(407)
Other programs	1,548	4,938	3,390
Research and discovery and unallocated costs			
Personnel related (including share-based compensation)	1,892	6,770	4,878
Facility and other	1,733	3,177	1,444
Total research and development expenses	\$16,206	\$32,527	\$16,321

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

Direct costs related to OTL-102 in 2017 consist of the costs of in-licensing the technology relevant to the program, which included our commitment to issue 437,049 ordinary shares to the licensor.

Direct research and development expenses relating to OTL-201 decreased by \$0.4 million in 2017. The decrease primarily relates to a decrease in in-licensing fees of \$3.0 million in 2017 as all in-licensing transactions relevant to this program took place in 2016. This decrease is offset by an increase in OTL-201 manufacturing costs of \$2.4 million and clinical costs of \$0.2 million, as a result of increasing clinical research activities.

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

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

[Table of Contents](#)*General and administrative expenses*

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

Other income (expense), net

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

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

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

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

[Table of Contents](#)

Research and development expenses

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

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

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

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

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

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

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

Direct research and development expenses relating to OTL-201 decreased by \$0.9 million in the six months ended June 30, 2018. The decrease primarily relates to a decrease of \$0.7 million in

[Table of Contents](#)

manufacturing and process development costs associated with our viral vector and cell manufacturing processes and a decrease of \$0.2 million in preclinical development expenses.

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

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

General and administrative expenses

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

Other income (expense), net

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

Liquidity and capital resources

From our inception through June 30, 2018, we did not generate any revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We currently have only one commercial product, Strimvelis, which we acquired from GSK in April 2018 and our product candidates are in various phases of preclinical and clinical development. We do not expect to generate significant revenue from sales of any products for several years, if

[Table of Contents](#)

at all. To date, we have financed our operations primarily with proceeds from the sale of convertible preferred shares and reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from CIRM.

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

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

Cash flows

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

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

Operating activities

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

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

[Table of Contents](#)

During the year ended December 31, 2016, operating activities used \$14.6 million of cash, primarily resulting from our net loss of \$19.1 million, offset by net cash provided by changes in our operating assets and liabilities of \$1.5 million and net non-cash charges of \$3.0 million, which included \$3.1 million for the issuance of our ordinary shares as non-cash in-license fees. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2016 is primarily due to the impact of a \$0.6 million increase in prepaid expenses and other current assets, offset by a \$0.7 million increase in accounts payable and a \$1.5 million increase in accrued expenses and other current liabilities. Net cash used in operating activities for the year ended December 31, 2016 included \$4.6 million of cash payments for in-licensing technology fees.

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

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

Investing activities

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

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

Financing activities

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

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

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

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

Funding requirements

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

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

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

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

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

[Table of Contents](#)

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

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

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

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

Contractual obligations and commitments

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

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

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

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

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

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

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

Under the GSK Agreement, we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired by GSK and OTL-101. We will pay a

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

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

Critical accounting policies and significant judgments and estimates

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

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

Fair value of asset acquisitions

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

Accrued research and development expenses

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

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

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

Fair value measurements—tranche obligations

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

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

Share-based compensation

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

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

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

Determination of the fair value of ordinary shares

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

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

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

[Table of Contents](#)

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

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

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

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

[Table of Contents](#)

Options granted

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

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

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

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

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

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

Grants of stock options under the 2016 Plan

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

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

Income taxes

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

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

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

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

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

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

Quantitative and qualitative disclosures about market risks

Interest rate sensitivity

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

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

Foreign currency exchange risk

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

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

We do not currently engage in currency hedging activities in order to reduce our currency exposure, but we may begin to do so in the future. Instruments that may be used to hedge

future risks include foreign currency forward and swap contracts. These instruments may be used to selectively manage risks, but there can be no assurance that we will be fully protected against material foreign currency fluctuations.

Emerging growth company status

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

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

Off-balance sheet arrangements

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

Recently issued accounting pronouncements

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

Business

Overview

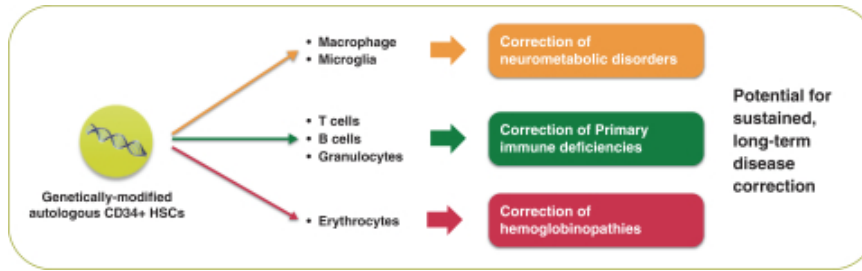
We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, HSCs into a gene-modified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

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

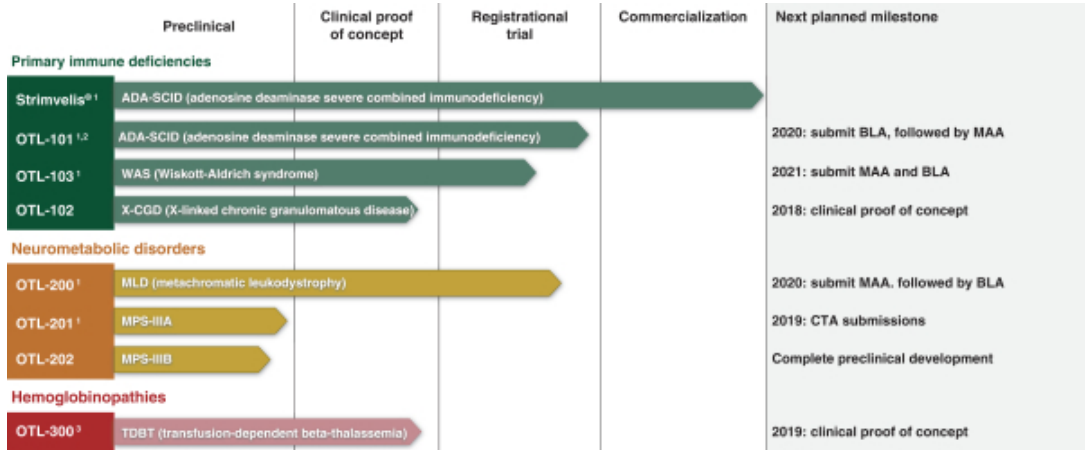
We are initially focusing our autologous *ex vivo* gene therapy approach on three therapeutic rare disease franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Our portfolio currently includes Strimvelis, our commercial-stage gammaretroviral-based product for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

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

We believe our approach of using lentiviral vectors to genetically modify HSCs has wide-ranging applicability to a large number of indications. The ability of HSCs to differentiate into multiple cell types allows us to deliver gene-modified cells to multiple physiological systems, including the central nervous system, immune system and red blood cell lineage, thereby potentially enabling the correction of a wide range of diseases. By leveraging the innate self-renewing capability of HSCs as well as the ability of lentiviral vectors to achieve stable integration of a modified gene into the chromosomes of HSCs, our gene therapies have the potential to provide a durable effect following a single administration.



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



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

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

We currently anticipate making submissions for regulatory approval of each of our three lead product candidates within the next three years. For each of these lead product candidates, we are in ongoing discussions with the applicable regulatory authorities with respect to the clinical and other data required for regulatory submission.

Table of Contents

As of September 2018, over 150 patients have been treated across our commercial and clinical-stage programs. The table below reflects the total number of patients treated the maximum follow-up and the range of patient follow-up as of September 2018 across the lead programs in our franchise areas.

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

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

The diseases we are targeting affect patients around the world, requiring an infrastructure to deliver gene therapies globally. We are therefore building a commercial-scale manufacturing infrastructure and leveraging technologies that will allow us to deliver our gene therapies globally in a fully-integrated manner. In order to meet anticipated demand for our growing pipeline of product candidates and planned product offerings, we are initially utilizing our existing network of CMOs to manufacture vectors and drug product. In addition, we currently operate two development laboratory facilities in California and plan to invest in additional facilities to accommodate our expanding technical operations and implement in-house drug product and vector manufacturing capabilities.

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

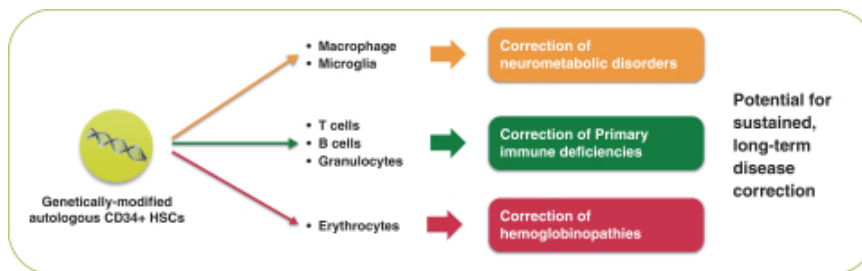
We have global commercial rights to Strimvelis and all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe, subject to obtaining necessary marketing approvals in those jurisdictions. We plan to deploy a focused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

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

Our autologous *ex vivo* gene therapy approach

Our *ex vivo* gene therapy approach seeks to transform a patient’s autologous HSCs into a gene-modified drug product to treat the patient’s disease. HSCs are self-renewing cells that are capable of differentiating into all types of blood cells, including white blood cells, red blood cells and platelets. HSCs can be obtained directly from the bone marrow, which requires administration of a general anesthetic, or from the patient’s peripheral blood with the use of a mobilizing agent that can move HSCs from the bone marrow into the peripheral blood. By delivering gene-modified HSCs back to patients, we seek to take advantage of the self-renewing capability of HSCs to enable a durable effect following a single administration, as has been seen in our development programs. In addition, the ability of HSCs to differentiate into multiple different cell types has the potential to enable the delivery of gene-modified cells to different physiological systems and allow the correction of a range of different diseases.

Clinical validation already exists for HSCT, an approach of treating a patient with HSCs contributed by a donor other than the patient that contain the properly functioning copy of the gene whose mutation has caused the underlying disease. However, this approach has significant limitations, including difficulties in finding appropriate genetically-matched donors and the risk of transplant-related rejection and mortality, and is therefore typically only offered on a limited basis. Our approach is intended to address the significant limitations of HSCT.

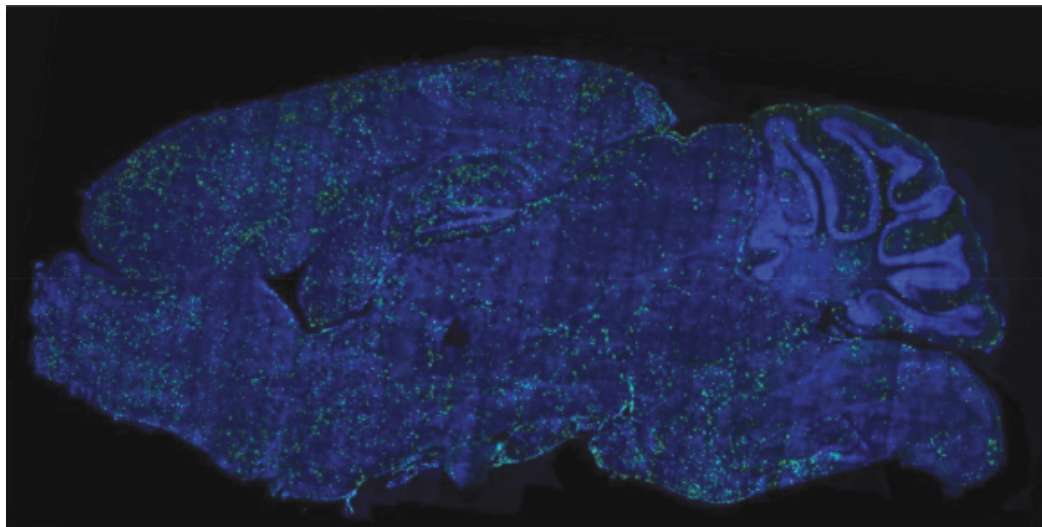


One example of the potential of our autologous *ex vivo* gene therapy approach to deliver genes to different physiological systems is demonstrated below. In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America*, or *PNAS*, a subpopulation of gene-modified HSCs have evidenced the potential to cross the blood-brain barrier, engraft in the brain as microglia and express genes and proteins within the central nervous system. As published in *PNAS*, the image below shows a cross-section of the brain of a mouse that received green fluorescent protein, or GFP, gene-modified HSCs intravenously. The GFP expression observed throughout the brain denotes the potential of gene-modified HSCs to cross the blood-brain barrier and express the functional protein

[Table of Contents](#)

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.

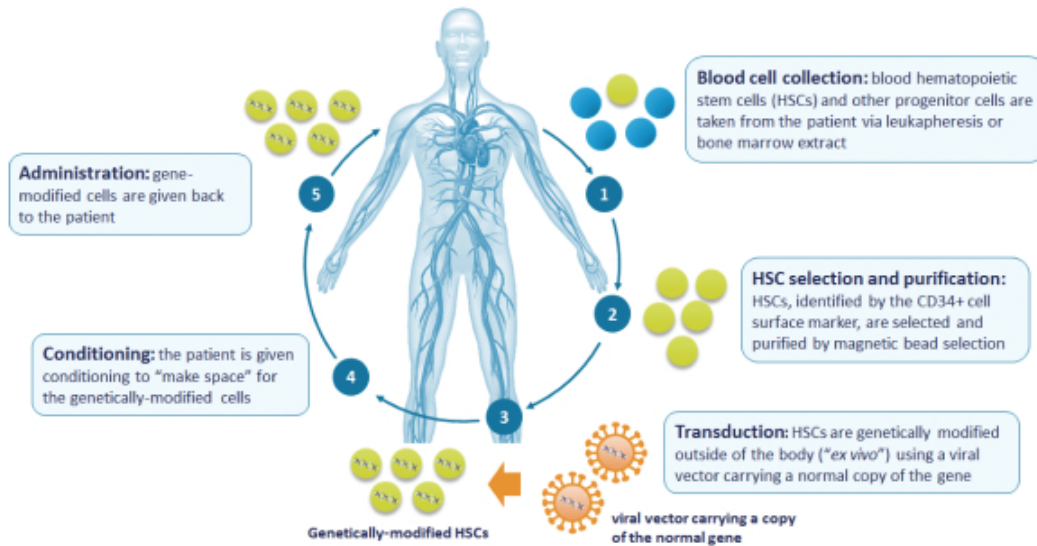
Transgene distribution in brain of mouse model following administration of HSCs transduced with GFP encoding vector



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.

Table of Contents

The image below illustrates the steps in our approach to transform a patient's autologous HSCs *ex vivo* into therapeutic product.



Initial clinical trials conducted using our product candidates utilized a fresh product formulation, resulting in a limited drug product shelf life. We plan to market our current and future product candidates, if approved, in a cryopreserved product formulation to enable the shipment of the drug product to specialized treatment centers throughout the world, allowing patients to receive treatment closer to their home. The cryopreservation also allows us to conduct a number of quality control tests on the modified HSCs prior to introducing them into the patient.

In addition, certain of our clinical-stage product candidates have been evaluated in registrational trials using drug product derived from HSCs extracted from the patients' bone marrow. To optimize our potential product label and commercial presence, as part of any BLA or MAA submission for such product candidates, we plan to demonstrate comparability between drug product manufactured using HSCs derived from the patients' peripheral blood and drug product manufactured using HSCs derived from the patients' bone marrow in these cases where clinical trials were conducted using vector and/or drug product manufactured at academic centers, we plan to demonstrate comparability between vector and/or drug product manufactured by our selected third party CMOs with vector and drug product manufactured at such academic centers.

Initially, we are employing our autologous *ex vivo* gene therapy approach to three target franchise areas: primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Data from clinical trials suggests that autologous *ex vivo* gene therapy has the potential to provide well-tolerated and sustainable results over existing standards of care for diseases in these target franchise areas. We believe that we can apply our approach beyond our initial target indications to treat a broad range of rare diseases.

Our strengths

We believe that the combination of our growing body of clinical data evidencing the potential of our autologous *ex vivo* gene therapy approach, and our deep expertise in the development,

manufacturing and commercialization of gene and cell therapies, positions us well to provide potentially transformative therapies through a single administration to patients suffering from a broad range of rare diseases. We believe our key strengths include:

- **Durable, sustained therapeutic potential:** Durable and sustained clinical activity has been observed in patients in each of our lead programs across five different diseases following a single administration. For example, our commercial-stage gammaretroviral program, Strimvelis, has demonstrated sustained recovery of the immune system, resulting in survival over approximately 18 years after a single administration. As of July 2018, overall survival has been observed in a maximum follow-up of approximately six years in patients treated with our lentiviral gene therapy OTL-101 for ADA-SCID and approximately eight years in patients treated with our lentiviral gene therapies OTL-200 for MLD and OTL-103 for WAS. Without treatment, these indications are almost always fatal early in life.
- **Demonstrated safety record:** Our autologous *ex vivo* gene therapy approach, has been well-tolerated in patients treated to date. Lentiviral vectors have a history of safety in clinical trials, with no reported instances of insertional mutagenesis or leukemogenesis in patients for more than 10 years. Our *ex vivo* modification of the patient's own HSCs also allows us to engineer and test the patient's cells prior to administering the therapy to the patient. Over 150 patients have been treated with our commercial product and clinical-stage product candidates, and each of these therapies has been well-tolerated overall, with no suspected unexpected serious adverse reactions, or SUSARs, related to the drug products observed to date. Of these over 150 patients, 127 patients were treated with our lentiviral-based clinical-stage programs. The most common adverse reactions observed in clinical trials across these programs have included pyrexia and infections. We believe that the long-term extensive follow-up across multiple different diseases and with vectors expressing different genes demonstrates the potential safety of our autologous *ex vivo* gene therapy approach.

Our autologous *ex vivo* gene therapy approach offers important advantages over HSCT, which is the standard of care for several of the indications that we are targeting. HSCT carries a significant risk of complications and mortality. In order to make bone marrow space for incoming donor cells, patients undergoing HSCT need to receive conditioning often involving two to three chemotherapy agents that are associated with significant short- and long-term organ toxicities. In our autologous *ex vivo* gene therapy approach, we employ a milder conditioning regimen, which is associated with reduced toxicity and length of hospitalization. HSCT also requires the identification of a well-matched third-party donor to provide the cells. A poor cell donor match can result in graft rejection or acute and chronic graft-versus-host disease, or GvHD, a serious complication of HSCT in which the third party donor's immune cells identify the cells of the patient as "foreign" and attack them. GvHD is a severe autoimmune reaction that can lead to organ failure and death. In general, a higher degree of mismatch between the donor and the recipient is associated with a greater risk of disease or graft rejection; however, a well-matched cell transplant can still result in GvHD. By using the patient's own cells, our autologous *ex vivo* gene therapies eliminate the risk of GvHD or graft rejection by providing the patient with a perfect cell match.

- **Applicability to a potentially large number of patients and indications:** A core part of our mission is to bring potentially transformative therapies to the broadest number of patients suffering from rare diseases. We believe our autologous *ex vivo* gene therapy approach has broad therapeutic potential across a large number of rare diseases in our target franchise areas. The lentiviral vectors that we employ in our clinical-stage programs have large capacity

payloads that have the potential to introduce a target gene of choice into the patient's HSCs. The transduction of these vectors into a patient's own HSCs allows for the potentially life-long production of gene-modified HSCs in the body and thus distribution of the target gene throughout multiple organs and tissues, including across the central nervous system.

- **Our deep expertise in gene therapy and rare diseases:** Our management team has over 100 years of collective experience in rare diseases and the manufacturing, preclinical and clinical development and commercialization of gene and cell therapies. Members of our executive leadership team have held senior positions at GSK, Shire, BioMarin, Alexion, Sangamo Therapeutics, PTC Therapeutics, StemCells Inc., Osiris, PCT Cell Therapy Services and other companies specializing in gene and cell therapies and rare diseases. In addition, we partner with academic institutions that are pioneers in autologous *ex vivo* gene therapy and we have obtained exclusive licenses to extensive preclinical data, clinical data and know-how to build our portfolio of autologous *ex vivo* gene therapies. These partnerships with leading institutions such as UCLA, Boston Children's Hospital and the NIH in the United States, and UCL, GOSH, Telethon Institute of Gene Therapy, San Raffaele Hospital, The University of Manchester, the Manchester Foundation Trust, and Généthon in Europe, are a core part of our research engine through which we are advancing our lead clinical-stage programs and working to identify opportunities with comparably high probabilities of success. We plan to leverage our internal expertise combined with our relationships with leading academic institutions to transition our lead clinical-stage product candidates from the academic setting to commercial-ready production and further expand our pipeline.

Our strategy

Our mission is to transform the lives of patients with rare genetic diseases using our autologous *ex vivo* gene therapy approach. We are building a leading, global, fully-integrated gene therapy company focused on serious and life-threatening rare diseases. To achieve this, we are pursuing the following strategies:

- **Advance our five clinical-stage product candidates towards marketing approvals:** Our pipeline currently includes five clinical-stage programs including three in advanced registrational trials. We plan to submit a BLA with the FDA for our product candidate OTL-101 for ADA-SCID in 2020, followed by an MAA with the EMA. Our programs OTL-200 for MLD and OTL-103 for WAS have both achieved their primary endpoints in registrational trials. Though the primary endpoints in these registrational trials have been achieved, patient follow-up remains ongoing in accordance with the trial protocols. We plan to submit an MAA for our product candidate OTL-200 with the EMA in 2020, followed by a BLA with the FDA, and we intend to submit an MAA with the EMA and a BLA with the FDA for our product candidate OTL-103 in 2021. Furthermore, our clinical-stage programs OTL-102 for X-CGD and OTL-300 for TDBT continue to be generally well-tolerated and generate clinical activity data in initial clinical trials, and, assuming these trials are successful, we plan to advance these programs through clinical development to regulatory submission.
- **Leverage the power of our therapeutic approach to expand our product pipeline across multiple indications:** Through our clinical trials, we believe we have exhibited the potential of our autologous *ex vivo* gene therapy approach to target multiple physiological systems in the human body, including the central nervous system, immune system and red blood cell lineage. We seek to leverage our academic collaborations and focus our preclinical and clinical research

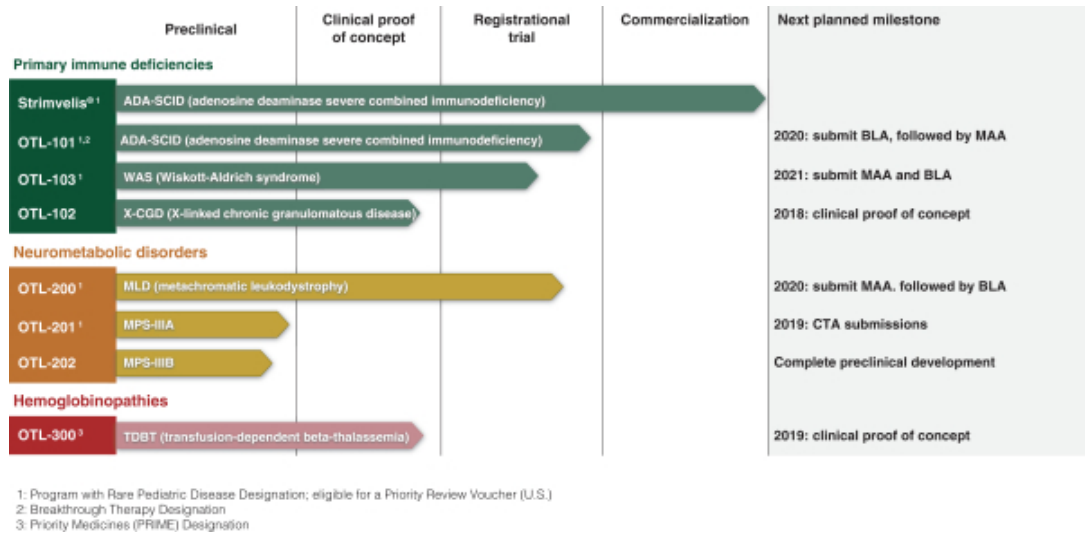
on rare disease indications with high unmet need and for which we believe there is a high probability of clinical success, based on the results observed in our clinical trials to date. For example, we are expanding our neurometabolic disorders franchise with the development of two preclinical programs, OTL-201 for MPS-III A and OTL-202 for MPS-III B. We anticipate submitting a CTA with the applicable regulatory authority in Europe for OTL-201 by the end of 2019 and plan to continue to progress preclinical development of OTL-202.

- **Establish an efficient and scalable manufacturing infrastructure:** The rare diseases we target affect patients around the world, and therefore we are building an infrastructure with the goal of delivering our gene therapies globally. To meet our near-term supply needs for initial commercialization primarily in the United States and Europe, we have established supply agreements with an international network of CMOs for vector manufacturing and for the production of drug product. We plan to invest in in-house manufacturing capabilities to accommodate our expanding process development and vector and drug product manufacturing activities and to continue building our international supply chain. We are also developing and implementing cryopreservation processes for our clinical-stage product candidates, which, in combination with our international network of CMOs and our planned in-house manufacturing capabilities, will help enable the distribution and administration of our gene therapies to wherever patients are located across the globe. In addition, we are investing in several initiatives to improve the efficiency of our manufacturing processes, including the automation of certain aspects of our production processes, with the goal of reducing production costs and our cost of goods. We are also executing on our plans for development of stable cell lines for OTL-102 and OTL-300. We believe that these initiatives will ultimately position us to deliver our gene therapy products efficiently and at a global scale commensurate with patient demand as our product offerings grow.
- **Establish a patient-centered, global commercial infrastructure:** We have global commercial rights to all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, subject to obtaining necessary marketing approvals. Leveraging the knowledge gained through our commercial product Strimvelis for ADA-SCID, and given our focus on rare genetic diseases, we plan to deploy a focused commercial infrastructure to deliver our product candidates to patients. In addition, we believe there is an urgent need to improve the early diagnosis of patients with rare genetic diseases, including those in our current focus areas, and we are implementing programs to improve patient and physician education regarding early access to transformative gene therapies for these conditions. We believe the value proposition for patients, caregivers, specialist physicians and payors is significant, given the potentially long-lasting benefits anticipated from our gene therapies. Accordingly, we are focused on working closely with all relevant stakeholders to ensure the widest possible post-approval access for our product candidates.
- **Execute a disciplined business development strategy to strengthen our portfolio of product candidates:** We have built our broad pipeline of product candidates through partnerships with leading academic institutions and through multiple successful in-licensing and acquisition deals. We will continue to evaluate new in-licensing opportunities and collaboration agreements with leading academic institutions and other biotechnology companies around programs that seek to address areas of high unmet need and for which we believe there is a high probability of clinical success, including programs beyond our target franchise areas and current technology footprint.

Our pipeline

Our advanced portfolio of autologous *ex vivo* gene therapies targets serious and life-threatening rare diseases, initially focusing on primary immune deficiencies, neurometabolic disorders and hemoglobinopathies. Over 150 patients have been treated as of September 2018 across our lead programs. Our primary immune deficiencies franchise consists of our commercial program, Strimvelis for ADA-SCID, two advanced registrational clinical programs, OTL-101 for ADA-SCID and OTL-103 for WAS, and one clinical-stage program, OTL-102 for X-CGD. Our neurometabolic disorders franchise consists of one advanced registrational clinical program, OTL-200 for MLD, and two preclinical programs, OTL-201 for MPS-IIIa and OTL-202 for MPS-IIIb. Our hemoglobinopathies franchise consists of one clinical-stage program, OTL-300 for TDBT.

The status of the lead pipeline programs is outlined below:



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

Gene therapy treatment of ADA-SCID

Disease overview

Severe combined immunodeficiency, or SCID, is a rare, life-threatening inherited disease of the immune system. ADA-SCID, commonly known as “bubble-baby disease”, is a specific form of SCID caused by mutations in the ADA gene, resulting in a lack of, or minimal, immune system

development, which leaves the patient vulnerable to severe and recurrent bacterial, viral and fungal infections. The first symptoms of ADA-SCID typically manifest during infancy with recurrent severe bacterial, viral and fungal infections and overall failure to thrive, and without treatment the condition can be fatal within the first two years of life. The lack of a functional ADA gene in ADA-SCID patients can also lead to neurological deficits involving motor function, deafness, hepatic dysfunction and eventual failure, and cognitive and behavioral dysfunction.

The incidence of ADA-SCID in the United States is currently estimated to be between one in 200,000 and one in 1 million live births. Higher incidence rates are reported in geographies of higher consanguinity, such as Turkey and the Middle-East.

Patients with ADA-SCID are most commonly diagnosed during the first six months of life based on recurrent bacterial, fungal, and viral infections, persistent lymphopenia, and ADA activity below 1%. Newborn screening for T-cell deficiencies, including ADA-SCID, has now been adopted in 49 states in the United States, as well as in Ontario, Israel, Taiwan and Norway.

Limitations of current therapies

The primary treatment options for ADA-SCID are HSCT and ERT. Although HSCT is a potentially curative treatment for ADA-SCID patients, this procedure is associated with a high risk of complications and mortality, with one-year survival rates of 43%, 67% and 86% for transplants from haploidentical donors, HLA-matched unrelated donors and HLA-matched sibling donors, respectively. HSCT also does not treat the cognitive and behavioral manifestations of ADA-SCID.

Chronic ERT is a palliative treatment for ADA-SCID patients and involves weekly or bi-weekly muscular infusions. ERT with pegylated adenosine deaminase has been approved by the FDA and is commercialized only in the United States. It is only available on an ad-hoc basis under compassionate use in Europe. Although ERT can temporarily restore immune function by maintaining high ADA levels in the plasma, many patients receiving chronic ERT therapy continue to have abnormally low levels of lymphocytes in the blood after the first year of treatment, and 50% of patients therefore require supplementary immunoglobulin replacement therapy. Chronic ERT is associated with a 78% survival rate at 20 years; however, significant morbidity or mortality may occur as early as one to three years after the first treatment. Patients on ERT may experience refractory hemolytic anemia, chronic pulmonary insufficiency, and lymphoproliferative disorders.

Our solutions, OTL-101 and Strimvelis for treatment of ADA-SCID

We are developing OTL-101 as an autologous *ex vivo* lentiviral gene therapy to sustainably treat patients with ADA-SCID through a single administration. OTL-101 is manufactured from HSCs isolated from the patient's own bone marrow or mobilized peripheral blood, and is modified to add a functional ADA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a mild conditioning regimen.

OTL-101 has been investigated in multiple clinical trials in the United States and Europe. As of September 2018, 61 patients have been treated with OTL-101 drug product, with a maximum follow-up of up to approximately 6.5 years post treatment. Based on our ongoing discussions with the FDA, we expect our BLA submission will include data from our UCLA registrational trial of 20 patients treated with a fresh product formulation, supportive data derived from at least five patients treated with a cryopreserved formulation at UCLA and additional data derived from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, as well as any other patients with adequate follow-up at the time of submission. See “—Regulatory Pathway

for OTL-101.” The remaining 26 patients treated as of September 2018 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this prospectus but for which safety data is presented in the summary below. Among the 61 patients treated so far, three patients, including one patient in the supportive UCLA trial, one patient in the additional GOSH trial and one in the compassionate use program, did not engraft and had to resume enzyme replacement therapy and/or receive rescue bone marrow transplant.

In the European Union, our commercial program Strimvelis is available as the only approved gene therapy option for patients with ADA-SCID. The EMA approved Strimvelis in May 2016 for treatment of children with ADA-SCID with no suitable HLA-matched stem cell donor. Strimvelis consists of HSCs transduced with a gammaretroviral vector, an earlier generation of vector for autologous ex vivo gene therapy, encoding the human adenosine deaminase cDNA sequence. Strimvelis is available in fresh product formulation at San Raffaele Hospital in Milan, Italy, and has a shelf-life of up to six hours. We plan to continue to make Strimvelis available to eligible patients as we advance OTL-101 as an autologous ex vivo lentiviral gene therapy for ADA-SCID.

We obtained worldwide rights to the OTL-101 program through our license agreement with UCLB and UCLA and we obtained worldwide rights to the Strimvelis program through the GSK Agreement.

OTL-101 has received orphan drug designation from the FDA and the EMA for the treatment of ADA-SCID and Breakthrough Therapy Designation from the FDA. OTL-101 has also received a Rare Pediatric Disease Designation from the FDA. We expect to submit a BLA for OTL-101 with the FDA in 2020, followed by an MAA submission with the EMA.

Ongoing registrational, supportive and additional clinical trials

OTL-101 has been evaluated in a registrational trial conducted by UCLA in the United States using a fresh product formulation and is being evaluated in an ongoing supportive clinical trial at UCLA using a cryopreserved formulation. These trials were initially conducted under an investigator-sponsored IND, which was subsequently transferred to us. A fresh product formulation is being evaluated in a concurrent additional investigator-sponsored clinical trial conducted by GOSH in Europe. Each of these clinical trials enrolled ADA-SCID patients between one month and 18 years of age who were ineligible for HSCT due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

Registrational trial at UCLA

Our anticipated rolling BLA submission for OTL-101 will include data from 20 enrolled and treated patients in a registrational trial at UCLA for which follow-up has recently completed. Production of the fresh OTL-101 drug product formulation (with bone marrow as the cellular source) used in this clinical trial was performed onsite at UCLA. In this clinical trial, all patients were treated with ERT prior to enrollment and continued ERT until 30 days following their initial treatment with OTL-101.

The primary goals of this clinical trial were to assess the safety and efficacy of OTL-101 in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial included immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates.

Overall survival and event-free survival of 100% was observed at 12 months post-treatment, the primary endpoint of the trial. None of the enrolled patients required rescue medication, HSCT, or resumption of ERT. Importantly, patients in this trial showed immune cell reconstitution

following treatment with OTL-101, which can lead to restoration of both cellular and humoral immune responses. This is reflected by the patients' ability to recover from infections beginning in the first six months following treatment. As of April 2017, the number of infections in evaluable patients decreased from 17 in the first year following treatment with OTL-101 to seven in the second year following treatment, and the number of serious infections in evaluable patients decreased from seven to one during the same period.

As summarized in the charts below, these patients' data were compared with a historical cohort of ADA-SCID patients, 0 to 18 years of age, who received treatment with allogeneic bone marrow transplant between 2000 and 2016 (n=26). These data were gathered retrospectively from Great Ormond Street Hospital and Duke University Hospital. Comparator populations from this group were ADA-SCID patients without a medically eligible HLA-matched sibling/family donor (HSCTWOUT), patients with an HLA-matched related donor (HSCTWITH) and the complete group (HSCTALL).

As summarized in the chart below, when comparing the overall survival for the OTL-101 treated patients with the historical control group, OTL-101 treated patients achieved higher overall survival rates at 12 months and 24 months (both at 100%) versus the combined group that received allogeneic bone marrow transplant 92.31% (95% CI: 75%-99%) at 12 months and 88% (95% CI: 69-97%) at 24 months. A confidence interval, or CI, is a range of values in which, statistically, there is a specified level of confidence that the true rate falls within this range. Small sample sizes will yield wider confidence intervals. In this trial, the results indicate that there is a 95% level of confidence that overall survival rates at 12 months were between 75% and 99%, which we represent as (95% CI: 75%-99%), and a 95% level of confidence that overall survival rates at 24 months were between 69% and 97%, which we represent as (95% CI: 69-97%).

OTL-101 (ADA-SCID): summary of Overall Survival (OS)

Overall Survival (OS) at 12 months (primary endpoint)			Overall Survival (OS) at 12 months		
	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)		Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (83.16, 100)	-	OTL-101 pivotal data	100% (78.20, 100)	-
HSCT without MRD	85.71% (57.19, 98.22)	14.29% (-5.40, 42.81)	HSCT without MRD	85.71% (57.19, 98.22)	14.29% (-8.99, 42.81)
HSCT with MRD	100% (73.54, 100)	-	HSCT with MRD	90.91% (58.72, 99.77)	9.09% (-14.24, 41.28)
All HSCT	92.31% (74.87, 99.05)	7.69% (-10.08, 25.13)	All HSCT	88% (68.78, 97.45)	12.00% (-12.18, 31.56)

As summarized in the chart below, event-free survival is defined as survival without resumption of PEG-ADA enzyme replacement therapy or need for rescue allogeneic HSCT. Event-free survival in the OTL-101 treatment group was 100% at 12 months and at 24 months. In comparison, event-free survival in the combined allogeneic HSCT group was 80.77% (95% CI: 60.7-93.5%) at 12 months and 56% (95% CI: 34.9-75.6%) at 24 months. For the primary comparator group, who received allogeneic HSCT without a matched related donor, event-free survival rates were 35.71% lower (95% CI: 11.21-64.86%) and 50% lower (95% CI: 20.70-76.96%) than the OTL-101 treated group at 12 months and 24 months, respectively. Because the 95% confidence intervals for these estimates of the difference from the OTL-101 treated group do not include zero, these are statistically meaningful differences between the OTL-101 treated group and the HSCT without a matched related donor comparator group. Similarly, event-free survival in the comparator HSCT group that received a matched related donor (the current standard of care)

was 36.36% lower (95% CI: 7.31-69.21%) than the OTL-101 treated group at 24 months. Because the 95% confidence intervals for this estimate does not include zero, this also represents a statistically meaningful difference between the OTL-101 treated group and the comparator HSCT with a matched related donor.

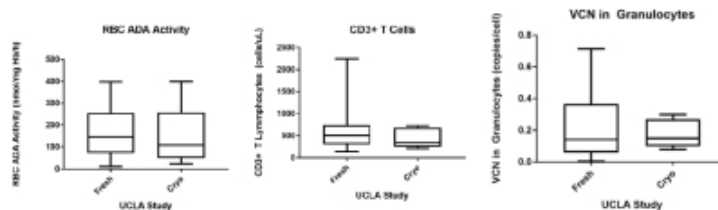
OTL-101 (ADA-SCID): summary of Event Free-Survival (EFS)

Event Free Survival (EFS) at 12 months (primary endpoint)			Event Free Survival (EFS) at 24 months		
	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)		Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (83.16, 100)	-	OTL-101 pivotal data	100% (78.20, 100)	-
HSCT without MRD	64.29% (35.14, 87.24)	35.71% (11.21, 64.86)	HSCT without MRD	50% (23.04, 76.96)	50% (20.70, 76.96)
HSCT with MRD	100% (73.54, 100)	-	HSCT with MRD	63.64% (30.79, 89.07)	36.36% (7.31, 69.21)
All HSCT	80.77% (60.65, 93.45)	19.23% (0.71, 39.35)	All HSCT	56% (34.93, 75.60)	44% (16.15, 65.07)

Ongoing supportive clinical trial with UCLA (with cryopreserved formulation)

A cryopreserved formulation of OTL-101 (with bone marrow as cellular source) is currently being evaluated in an ongoing supportive clinical trial at UCLA. Enrollment for this trial is complete; 10 patients have been treated, with currently available follow-up data of between 2.9 months to 9.3 months, as of January 2018. One patient treated in this trial did not engraft and had to resume enzyme replacement therapy and/or receive rescue bone marrow transplant. The aim of this clinical trial is to assess the success of treatment at the patient level, referred to as a responder analysis, at six-months post-treatment, using predictive criteria for overall survival and event free survival.

In this trial, ADA activity, vector copy number, or VCN, and CD3+ T-cell counts at six months post-treatment are measured as key biological correlates of efficacy and compared with the results obtained from our registrational trial with fresh product formulation. We expect to use these data to support the analytical comparability analysis between fresh and cryopreserved formulations that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively. Data from the first five patients that successfully engrafted and achieved the six month post-treatment follow-up date shows similarity in these biological correlates of efficacy measured in patients from the UCLA fresh trial (n=10) at 6 months. We believe this consistency between the UCLA fresh and cryopreserved studies is supportive of ongoing analytical comparability data between the fresh and cryopreserved formulations of OTL-101. We are continuing to evaluate the data from this ongoing trial and will include the data available at the time of submission to support our BLA and MAA submissions.



RBC = red blood cells; ADA = adenosine deaminase; VCN = vector copy number. The figure shows data for UCLA Fresh trial patients ("Fresh", n = 20) and UCLA Cryo trial with 5 evaluable patients ("Cryo", n = 5) at 6 months of follow-up. The boxes indicate the median and inter-quartile range, the 'whiskers' are the minimum and maximum values for each group.

Additional clinical data from GOSH

In a parallel investigator-sponsored trial being conducted by GOSH, 10 enrolled patients have been treated with fresh product formulation (with bone marrow and mobilized peripheral blood as the cellular source). The drug product used in this clinical trial is produced using the same vector as at UCLA but with a manufacturing process with minor differences to that for OTL-101. Production of the fresh formulation of the drug product used in this clinical trial was performed onsite at GOSH. In this clinical trial, all patients were being treated with ERT prior to enrollment and all but one patient continued ERT until 30 days following initial treatment with autologous ex vivo HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates.

As of September 2017, overall survival of 100% has been observed at 12 months post treatment in the 10 patients enrolled, and nine patients have achieved event-free survival, with only one patient resuming ERT after 12.2 months due to a failure to engraft. We believe this failure to engraft may in part be attributable to the patient's early discontinuation of ERT prior to treatment in contravention of the trial protocol, but may also relate to other clinical factors.

Importantly, patients in this trial showed immune reconstitution following treatment with the drug product, which can lead to restoration of both cellular and humoral immune responses. This is reflected by the patients' ability to recover from infections beginning in the first six months following treatment. As of March 2017, the number of infections in evaluable patients decreased from 16 in the first year following treatment to two in each of the second and third years following treatment, and the number of serious infections in evaluable patients decreased from two in the first year following treatment to zero and one in the second and third years, respectively.

There is a second investigator-sponsored trial being conducted by GOSH, aiming to enroll 10 patients treated with cryopreserved product formulation with mobilized peripheral blood as the cellular source. The drug product used in this clinical trial is produced using the same vector and same manufacturing process as the drug product being evaluated at UCLA. Production of the cryopreserved formulation of the drug product used in this clinical trial is performed onsite at GOSH. In this clinical trial, all patients are being treated with ERT prior to enrollment and continue ERT until 30 days following initial treatment with autologous ex vivo HSC gene therapy.

The primary goals of this clinical trial are to assess the safety and efficacy of the investigational drug product in ADA-SCID patients, as measured by overall survival and event-free survival at 12 months post-treatment. Secondary goals in this clinical trial include immune reconstitution, as measured by lymphocyte and immunoglobulin levels, and reduction in severe infection rates. As of September 14, 2018, five patients have been treated and are alive and off of ERT.

OTL-101 Program Safety

As of September 2018, safety data from the 20 patients treated in the registrational trial in the United States indicate that OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis in follow-ups ranging from 19.2 months to 33 months. There were 51 SAEs reported, 14 of which were assessed by the investigator as being possibly related to protocol treatment or procedures. One of these SAEs was a staphylococcal infection from the transduced bone marrow cells. The patient was treated with antibiotics and recovered. The most common SAEs were

pyrexia, infections and gastrointestinal disorders. There were no adverse events, or AEs, or SAEs leading to the withdrawal of patients from the trial. All SAEs resolved with standard of care treatment. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR.

As of September 2018, safety data from the 10 patients treated in the supportive clinical trial with UCLA in the United States and from the two compassionate use patients receiving a cryopreserved formulation, indicate OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis up to 1.5 years post treatment. There were 14 SAEs reported in the UCLA supportive clinical trial, three of which (two events of leukopenia and one event of neutropenia in the same patient) were assessed by the investigator as being related to the protocol treatment or procedures and were the result of the patient's failure to achieve engraftment. In the compassionate use program, 5 SAEs were reported and were not deemed to be related to OTL-101. The most common SAEs across the UCLA supportive clinical and United States compassionate use program were leukopenia, pyrexia, and infections. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR.

In Europe, as of September 2018, safety data from the 10 patients treated in the additional clinical trial with GOSH and from the 10 compassionate use patients, indicate that the investigational drug product was generally well-tolerated, with no instances of insertional mutagenesis up to six years post treatment. There were 25 SAEs reported in the additional clinical trial with GOSH, none of which were assessed by the investigator as being possible related to the protocol treatment or procedures, and six SAEs reported in the compassionate use program, one of which, a product contamination, was deemed by the investigator as being possibly related to protocol treatment or procedures. This SAE was a staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product during the transduction procedure at this academic facility. The most common SAEs across the additional clinical trial and compassionate use program were pyrexia, infections and immune system disorders. There were no AEs or SAEs leading to the withdrawal of patients from the additional clinical trial and compassionate use program. All SAEs resolved with standard of care treatment. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR. In a cryopreserved study protocol in the United Kingdom, where five of ten patients have been recently treated, there were two SAEs reported, neither of which were deemed to be related to the drug product. In three patients treated under compassionate use with cryopreserved formulation, nine SAEs have been reported, none of which were deemed to be related to the product.

Regulatory Pathway for OTL-101

We are currently in discussions with the FDA to finalize the requirements for our planned BLA submission for OTL-101 in 2020. Based on these discussions, we currently expect that our BLA submission will include clinical data from a registrational trial of 20 patients treated with a fresh product formulation at UCLA, supportive data derived from at least five patients treated with a cryopreserved formulation at UCLA, additional data from a clinical trial of 10 patients treated with a fresh product formulation at GOSH, and any other patients with adequate follow-up at the time of submission. Prior to completion of our BLA submission for OTL-101, we will be required to prepare a final clinical trial report for our registrational trial, as well as our supportive clinical trial to support the analytical comparability data between fresh and cryopreserved drug product formulations. We expect to have further discussion with FDA regarding our CMC data package.

Ultimately, the FDA will determine whether or the extent to which those data may be included in an application for marketing approval or even if included, the extent such data is considered for assessment of quality, safety, efficacy of the drug product candidate. We expect to have an additional CMC-focused meeting with the FDA prior to our BLA submission to discuss analytical comparability between academic and commercial manufacturing processes, vector and drug product process characterization and process validation approach, including demonstration of manufacturing state of control. We also plan to discuss with the FDA the data required for the inclusion of patients' mobilized peripheral blood as the cellular source material, together with patient bone marrow, in the label for OTL-101, if approved. Pending the outcome of these discussions, we may elect to initially seek approval of OTL-101 using patient bone marrow and subsequently seek approval for the use of mobilized peripheral blood. Although we currently expect to submit our BLA by 2020, our discussions with FDA are ongoing and we do not yet have definitive feedback from the FDA on the scope or adequacy of the requisite data necessary to support an approval and additional analytical comparability or clinical data may be required. See "Risk factors – The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates," "Risk factors – We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product" and "Risk factors – To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites."

Gene therapy for treatment of MLD

Disease overview

MLD is a rare and rapidly progressive neurometabolic disorder. MLD is caused by a mutation in the ARSA gene, leading to a deficiency in the ARSA enzyme and the accumulation of sulfatides and the progressive destruction in myelin-forming neurons in central and peripheral nervous systems and in visceral organs. Prognosis is severe, with continuous neurodegeneration and rapid deterioration of motor functions and cognitive impairment. In late-infantile MLD, the most common and severe form of the disease representing approximately 40-60% of all MLD patients, symptoms are generally first observed before three years of age, and the rate of mortality by five years of age is estimated at 50%. In juvenile MLD, representing approximately 20-35% of all MLD patients, symptoms are generally first observed between three and 16 years of age, and the rate of mortality at ten years of age is estimated at 44%. In adult MLD, representing approximately 10-25% of all MLD patients, the onset of symptoms generally occurs after 16 years of age. Prognosis is severe, with continuous neurodegeneration and rapid progression of motor and cognitive impairment. Symptoms often manifest in late-infantile and early-juvenile MLD patients as incorrect gait and missed development milestones. Adult-onset MLD is often diagnosed through cognitive, behavioral and psychiatric pathologies, such as alcohol or drug use, or difficulty managing emotions resulting in psychiatric evaluation. MLD patients may also demonstrate bewilderment, inappropriate response to their surroundings, paranoia, dementia or auditory hallucinations.

The incidence of MLD is currently estimated at between 1.4 in 100,000 and 1.8 in 100,000 live births per year.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MLD. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well

as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MLD but does not slow or reverse the progression of the underlying disease. HSCT has limited and variable efficacy in arresting disease progression and, as a result, HSCT is not considered to be a standard of care for this disease. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MLD patients, their caregivers and families and healthcare systems.

Our solution, OTL-200 for treatment of MLD

We are developing OTL-200 as an autologous *ex vivo* lentiviral gene therapy to sustainably treat patients with MLD through a single administration. OTL-200 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood or bone marrow, modified to add a functional ARSA gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen. The gene-modified HSCs have the capacity to migrate to the brain, differentiate into microglia in the brain tissue and secrete the ARSA enzyme to treat the disease within the central nervous system.

To date, we have treated only late infantile and early juvenile patients in our clinical trials of OTL-200. As of September 2018, a total of 31 patients have been treated with OTL-200 drug product, with a maximum follow-up of up to approximately eight years post treatment, comprised of 20 patients in our registrational trial with a fresh product formulation, two patients in our supportive study with a cryopreserved formulation and nine patients treated under a compassionate use program with a fresh product formulation. Based on our clinical data to date, we believe OTL-200 has shown the potential to maintain motor function and intelligence quotient, or IQ, in patients.

We obtained worldwide rights to this program through the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored CTA, which we expect will be transferred to us by the end of 2018.

OTL-200 has received orphan drug designation from the FDA and the EMA for the treatment of MLD. OTL-200 has also received Rare Pediatric Disease Designation from the FDA. We plan to submit an MAA for OTL-200 with the EMA in 2020, followed by a BLA with the FDA.

Registrational trial

Our anticipated MAA and BLA submissions for OTL-200 will be supported by data from 20 patients with pre-symptomatic late infantile MLD, or pre- to early-symptomatic early juvenile MLD, currently enrolled and treated in a registrational trial at San Raffaele Hospital in Milan, Italy, for which follow-up is ongoing. In this registrational trial, all patients have achieved the primary endpoint at 24 months follow-up. In addition to the 20 patients treated with OTL-200 in this clinical trial, nine patients were treated under compassionate use programs at San Raffaele Hospital, which followed the same protocol as that used in the clinical trial. Manufacture of the fresh OTL-200 drug product formulation (with bone marrow as cellular source) was performed by a third-party commercial CMO.

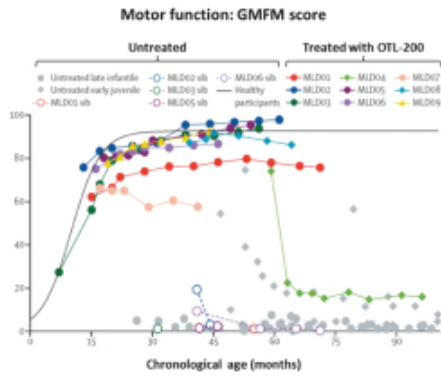
The primary goals of this clinical trial were to assess the efficacy and safety of OTL-200 in MLD patients, as measured by gross motor function and ARSA activity levels in the patients' blood cells 24 months post-treatment, as well as overall survival. Secondary goals for this clinical trial included assessment of cognitive function through IQ. The trial also provides for a follow-up period ending at 36 months' post-treatment.

Interim data from an ad hoc analysis of the first nine patients in this registrational trial was published in *Lancet Neurology* in 2016 and is set forth below. For purposes of this analysis, these interim data were presented in contrast to data from a historical cohort of 21 patients with late-infantile MLD and nine patients with early-juvenile MLD who had not received treatment, and to

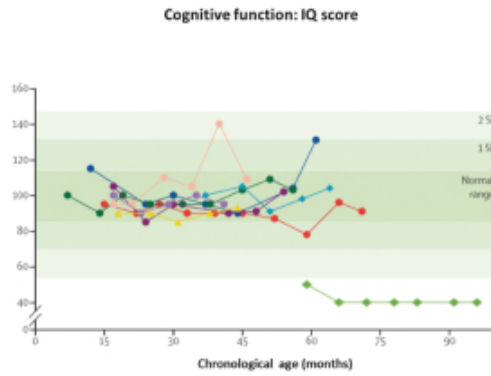
data from a cohort of 34 healthy children. Of the nine patients treated with OTL-200, six had late-infantile disease, two had early-juvenile disease and one had early-onset disease that could not be definitively classified.

In this interim analysis, eight patients treated with OTL-200, seven of whom received treatment when pre-symptomatic, had prevention of disease onset or halted disease progression, as compared with patients in the natural history group, most of whom experienced rapid disease progression. In addition, the gross motor function measure score, or GMFM score, for six patients up to the last follow-up showed that gross motor performance was similar to that of normally developing children. Neurocognitive development as measured by IQ score was within the normal range for eight patients, as compared to the natural course of the disease in untreated patients with early-onset MLD (data not shown in the publication). Also, IQ values of untreated patients all fell below the minimum value of 40 since first available testing (data not shown in the publication).

OTL-200 (MLD): Demonstrated Clinical Benefit for Motor and Cognitive Function



Motor function stable or comparable to healthy participants in 7/9 patients

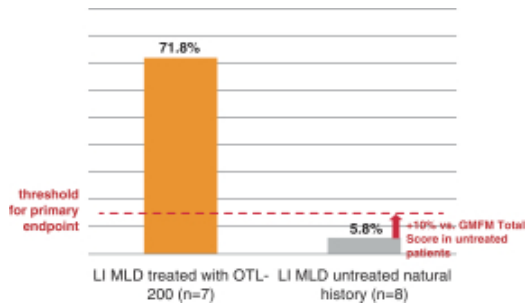


Cognitive function within normal range in 8/9 patients

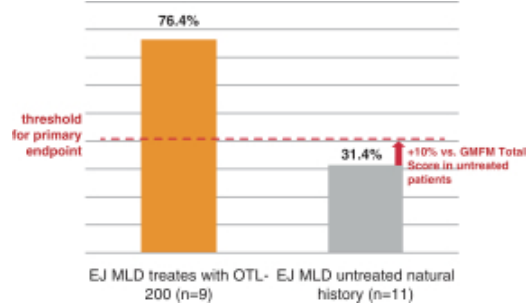
Presented below are efficacy data from a more recent interim analysis of all 20 patients treated in this clinical trial as of December 2017, the date of the most recent interim efficacy data report available to us. Motor function was measured in this trial with a GMFM score, which measures a child’s ability to perform standard motor tasks including lying and rolling, sitting, crawling and kneeling, standing, and walking, and running and jumping. A GMFM score of approximately 100% is representative of an individual with normal motor function. Following treatment with OTL-200, preliminary data indicate GMFM scores comparable to healthy individuals in seven out of nine late infantile patients, with a follow-up of up to three years. This primary endpoint was deemed to be achieved if there was a 10 percentage point improvement in GMFM scores compared to the untreated MLD natural history population at 24 months. Improvement in motor function has been observed in patients treated with OTL-200 compared to natural history patient data. At 24 months post-treatment, an average GMFM score of 71.8% was observed in late infantile patients (n=9) treated in this clinical trial compared to 5.8% in the untreated natural history population. For early juvenile patients treated in this clinical trial (n=11), an average GMFM score of 76.4% was observed at 24 months post-treatment, compared to 31.5% in the natural history population.

OTL-200 (MLD): GMFM Total Score

GMFM Total Score in late infantile MLD at 24 months post OTL-200 vs. natural history



GMFM Total Score in early juvenile MLD at 24 months post OTL-200 vs. natural history



In addition, OTL-200 evidenced increases in ARSA levels in most patients to within the normal range, as measured at three months post-treatment, achieving levels that fluctuated within or above the normal range throughout the duration of the follow-up. This co-primary endpoint was deemed to be achieved if ARSA values exceeded two standard deviations from baseline. Sustained ARSA levels well above two standard deviations post-treatment were observed in all patients in this trial.

Cognitive function in patients treated with OTL-200 has been measured using the IQ score. The stability or deterioration of a patient’s cognitive abilities were monitored using the neuropsychological tests administered according to the chronological age of the patient. Each neuropsychological instrument includes multiple core tests and supplemental subtests that comprise composite scores in specified cognitive areas. Following treatment with OTL-200, seven of the nine (78%) late infantile patients remained within normal ranges and seven of the eleven (64%) early juvenile patients had an IQ either within, close to or above the normal range.

As of March 2018, the date of the most recent safety report available to us, overall survival has been observed in 18 of 20 patients enrolled in the study, with a maximum follow-up of up to approximately 7.5 years and a median follow-up of approximately 4 years. Two patients with early juvenile MLD that were symptomatic at the time of treatment died from advanced disease progression that was deemed to be unrelated to the treatment by the investigator. From the 20

patients treated in the clinical trial indicate OTL-200 was generally well-tolerated, with no instances of insertional mutagenesis up to eight years post-treatment. 31 SAEs were reported in the patients in the clinical trial, none of which were assessed by the investigator to be related to OTL-200. In addition, as of March 2018, nine patients were treated under compassionate use, all of whom are alive; six SAEs were reported, none of which were assessed by the investigator to be related to the drug product. Across the program, the most common SAEs were motor dysfunction, dysphagia, vomiting and infections. There were no OTL-200 related SAEs. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in the clinical trial of any SUSAR.

Ongoing cryopreservation supportive clinical trial

A cryopreserved formulation of OTL-200 (with bone marrow as cellular source) is currently being evaluated in an ongoing clinical trial of pediatric patients with pre-symptomatic early onset MLD in Milan, Italy. Enrollment for this trial is ongoing, with two patients enrolled as of September 2018 and up to 10 patients expected to be enrolled.

The primary goal of this clinical trial is to assess the safety and efficacy of a cryopreserved formulation of OTL-200 in MLD patients, as measured by improvement in gross motor function and ARSA activity levels in the patients' blood cells as well as overall survival. Secondary goals for this clinical trial include assessment of cognitive function through IQ.

The first patient in this trial was treated in March 2018, and as of July 2018, the patient tolerated the administration well and has shown evidence of engraftment with supranormal production of ARSA.

We expect to use these clinical data to support the analytical comparability analyses between fresh and cryopreserved formulations that we plan to submit to the FDA and EMA as part of our BLA and MAA submissions, respectively.

Regulatory Pathway for OTL-200

We are currently in discussions with the EMA to finalize the requirements for our planned MAA submission for OTL-200 in 2020. Based on these discussions, we currently expect that our MAA submission will include clinical data from a registrational trial of 20 late infantile and early juvenile MLD patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as any other patients with adequate follow-up at the time of submission, treated with a fresh product formulation under compassionate use. Prior to completion of our MAA for OTL-200, we will be required to prepare a clinical trial report for our registrational trial, as well as our supportive clinical trial with cryopreserved formulation to support analytical comparability between fresh and cryopreserved drug product formulations. We expect to have a follow-up scientific advice and a pre-MAA meeting with the EMA to discuss the targeted label, last elements of comparability between fresh and cryopreserved formulations manufacturing processes as well as between drug product manufactured using HSCs derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow. A paediatric investigational plan compliance check will also need to be completed. Although we currently expect to complete our MAA submission in 2020, our discussions with EMA are ongoing and we do not yet have definitive feedback from the EMA

on the scope or adequacy of the requisite data necessary to justify an approval. See “Risk factors—The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates,” and “Risk factors—We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

Gene therapy for treatment of WAS

Disease overview

WAS is a rare, life-threatening inherited disease affecting the patient’s immune system and platelets leading to recurrent, severe infections and uncontrollable bleeds, which are the leading causes of death in the disease. WAS is referred to as an “X-linked-recessive” disease as it is associated with a genetic defect on the X chromosome. Because it is an X-linked disease, it affects mainly males. Patients with WAS are born with a defect in the gene that produces the WAS protein, or WASP. As a result, they suffer from life-threatening thrombocytopenia and are at risk of severe bleeds, infections, autoimmunity, malignancies and severe eczema. These symptoms require increasingly frequent hospitalizations. The median survival for a patient with WAS is approximately 15 years with patients with early onset WAS generally having a shorter life expectancy.

The incidence of WAS is currently estimated at approximately four in 1 million live male births.

Limitations of current therapies

Treatment options for WAS include conservative care with prophylactic anti-infective medicines, which are not always effective in preventing severe infections requiring antibiotics, antivirals, antifungals and intravenous immunoglobulin, as well as chronic platelet transfusions to prevent severe bleeding. WAS patients often are prescribed chronic oral medications or topical steroids and may require admission to hospital for intravenous antibiotic treatment. HSCT is an alternative treatment option for some patients for whom a sufficiently well-matched donor is identified. Although HSCT is potentially curative in patients with WAS, this approach can be associated with significant risks, especially when perfectly-matched cell donors are not available. Approximately 75% of WAS patients treated with HSCT experience serious complications, such as severe infections requiring hospitalization, autoimmune manifestations, and GvHD, within the first year of receiving the treatment.

Our solution, OTL-103 for treatment of WAS

We are developing OTL-103 as an autologous *ex vivo* lentiviral gene therapy to treat patients with WAS through a single administration. OTL-103 is manufactured from HSCs isolated from the patient’s peripheral blood or bone marrow that are modified to add a functional WASP gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a milder conditioning regimen compared to HSCT.

As of September 2018, eight patients have been treated with OTL-103 in an ongoing registrational trial and eight patients in a compassionate use program, with a maximum follow-up of up to approximately eight years post-treatment.

We obtained worldwide rights to this program through the GSK Agreement. The clinical trials for this program have been conducted under a GSK-sponsored CTA, which was transferred to us in August 2018.

OTL-103 has received orphan drug designation from the FDA and the EMA for the treatment of WAS. OTL-103 has also received a Rare Pediatric Disease Designation from the FDA. We plan to submit an MAA with the EMA and a BLA with the FDA for our OTL-103 for the treatment of WAS in 2021.

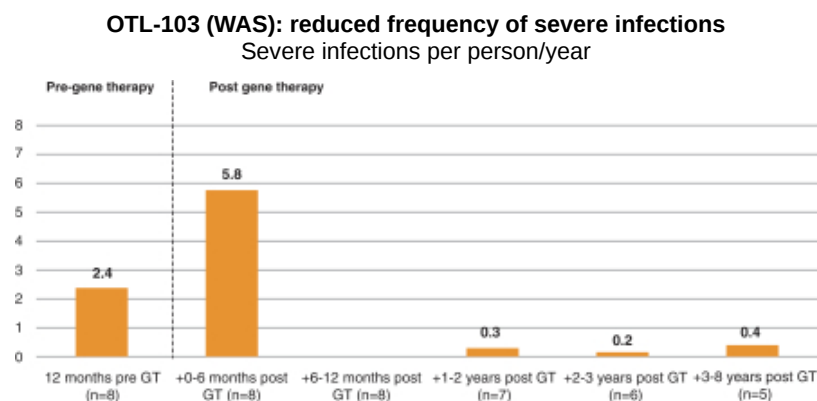
Registrational trial

Our anticipated MAA and BLA submissions for OTL-103 will include data from eight currently enrolled patients treated with a fresh product formulation in a registrational trial at San Raffaele Hospital for which follow-up is ongoing. The primary analysis for this registrational trial is prospectively defined to be when all patients have completed three years' follow-up. The eighth and final patient in this trial is expected to reach three years' follow-up by the end of September 2018. Manufacture of the fresh OTL-103 drug product formulation (with bone marrow or mobilized peripheral blood as the cellular source) was performed by a third-party commercial CMO. Data from the registrational trial will be supported by eight patients dosed in a compassionate use program. Based on discussions with the EMA, we intend to submit data to the EMA from additional patients treated with a cryopreserved formulation.

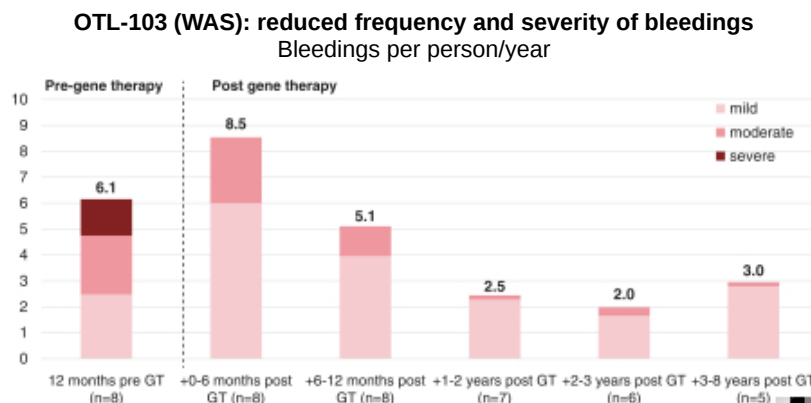
Patients treated in the registrational trial and compassionate use program were below the age of 12 years with a diagnosis of severe, classical WAS and were ineligible for HSCT treatment due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

The primary goals of this clinical trial are to assess the efficacy and safety of OTL-103 in WAS patients, as measured by, for example, improved T-cell function, improved platelet count and overall survival at 36 months. Secondary goals of this clinical trial include reduced bleeding episodes and reduced frequency of infections.

As of April 2016, the date of the most recent interim data report available to us, WASP expression in lymphocytes and platelets was substantially improved compared to baseline by six months and remain constant thereafter. At one year post-treatment with OTL-103, T-cell counts increased in all seven evaluable patients, as compared to counts prior to treatment, reaching normal values. Because of the increase in T-cells, a reduction in infections was observed in patients post-treatment compared to one year prior to treatment with OTL-103.



Mean platelet counts before treatment were low, with a range of 6–25 x 10⁹ 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 10⁹ per liter, and further increases in platelet count were observed in six patients to a range of 27–169 x 10⁹ 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.



As of March 2018, the date of the most recent safety report available to us, 100% overall survival has been observed in the eight patients treated in the clinical trial, with a maximum follow-up of up to 7.8 years and a median follow-up of 5.7 years. Safety data from the eight patients treated in this registrational clinical trial indicate OTL-103 was well-tolerated, with no instances of insertional mutagenesis. There were 29 SAEs reported within the trial, none of which were assessed by the investigator as being related to OTL-103. Five SAEs were reported in seven patients treated under compassionate use, none of which were assessed by the investigator as being related to OTL-103. One of these compassionate use patients died as a consequence of a pre-existing neurological disease. That event was deemed to be unrelated to the product. The remaining six compassionate use patients are alive. Across the program, the most common SAEs were pyrexia, infections, electrolyte imbalance, food allergy and neutropenia. There were no OTL-103 related SAEs leading to the withdrawal of patients from the trial. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator of any SUSAR.

Regulatory Pathway for OTL-103

We are currently in discussions with EMA and FDA to finalize the requirements for our planned MAA and BLA submissions, respectively, for OTL-103 in 2021. We currently expect that our MAA and BLA submissions will include clinical data from a registrational trial of 8 patients treated with a fresh product formulation at San Raffaele Hospital in Milan, Italy, and supportive data derived from patients treated with a cryopreserved formulation at San Raffaele Hospital in Milan, Italy, as well as additional patients with adequate follow-up at the time of submission, treated with a fresh product formulation under compassionate use. In addition, prior to completion of our MAA and BLA for OTL-103, we will need to collect clinical data with a cryopreserved formulation. We

will also be required to prepare a clinical trial report for our registrational trial, as well as our supportive clinical trial with cryopreserved formulation to support analytical comparability between fresh and cryopreserved drug product formulations. We expect to have meetings with EMA and FDA, including a pre-MAA and a pre-BLA meeting, to obtain their concurrence on the appropriate data to support our marketing authorization application. Although we currently expect to complete our MAA and BLA submission by 2021, our discussions with EMA and FDA are ongoing and we do not yet have definitive feedback from the EMA and FDA on the scope or adequacy of the requisite data necessary to justify an approval. See “Risk factors – The results from our clinical trials for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates,” and “Risk factors – We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

Gene therapy for X-CGD

Disease overview

X-CGD is a rare, life-threatening inherited disease of the immune system. X-CGD is an X-linked-recessive disease and therefore affects males. Because of the underlying genetic defect in the cytochrome B-245 beta chain, or CYBB, gene in patients with X-CGD, the patient’s white blood cells, specifically neutrophils/granulocytes, are unable to kill bacteria and fungi, leading to repeated chronic infections. The main clinical manifestations of X-CGD are pyoderma; pneumonia; colitis; lymphadenitis; brain, lung and liver abscesses; and osteomyelitis. Granuloma formation can also occur as a result of persistent inflammatory response to the pathogens and can result in recurrent obstructions of the gastro-intestinal and urinary tract. Patients with X-CGD typically start to develop infections in the first decade of life. Mortality in X-CGD has been estimated at approximately 40% by the age of 35 years.

The incidence of X-CGD is currently estimated to be between 2.6 in 1 million and 10 in 1 million male live births.

Limitations of current therapies

Current treatment options for X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma, which are not always effective in preventing severe infections. Although HSCT is potentially curative in patients with X-CGD, this approach can be associated with significant risks, especially when well-matched cell donors are not available.

Our solution, OTL-102 for treatment of X-CGD

We are developing OTL-102 as an autologous *ex vivo* lentiviral gene therapy to treat patients with X-CGD through a single administration. OTL-102 is manufactured from HSCs isolated from the patient’s own mobilized peripheral blood or bone marrow, then modified to add a functional CYBB gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intravenous infusion following treatment with a myeloablative conditioning regimen.

OTL-102 is currently being investigated in ongoing investigator-sponsored clinical trials in the United States and in Europe and has evidenced sustained CYBB expression for over one year in four patients to date, with a follow-up for over two years post-treatment in the first successfully treated patient.

We obtained worldwide rights to the OTL-102 program through an option and license agreement with Généthon, pursuant to which we have exercised an option to certain intellectual property and clinical data associated with clinical trials sponsored by Généthon at sites in the United States and the United Kingdom and we continue to have the right to exercise an exclusive option with respect to an ongoing clinical trial conducted in France, which option expires in June 2019.

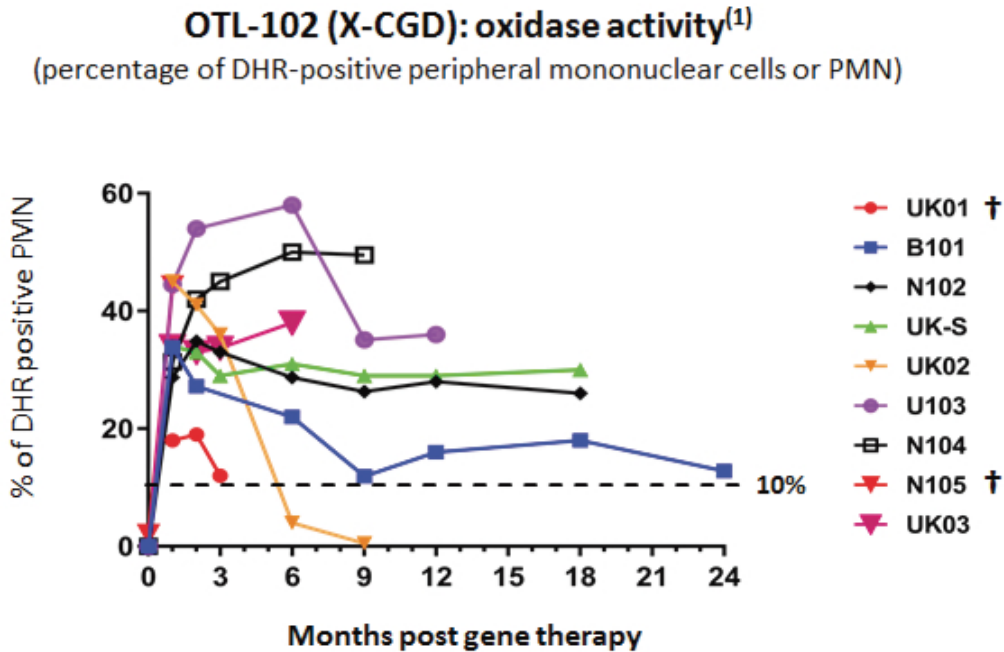
OTL-102 has received orphan drug designation from the EMA for the treatment of X-CGD.

Ongoing clinical trials

OTL-102 is currently being investigated in two ongoing investigator-sponsored proof of concept clinical trials in the United States and in Europe, with target enrollment of 10 patients in a clinical trial conducted by UCLA in the United States and target enrollment of five patients in a clinical trial conducted by GOSH in Europe. The clinical trial sites include Boston Children's Hospital, the NIH, and UCLA in the United States, and GOSH and The Royal Free Hospital in London. Manufacture of the drug product occurred at each of these sites using the same vector. As of January 2018, five patients have been treated in the clinical trial in the United States four of which were treated with a fresh product formulation and one of which was treated with a cryopreserved formulation, and three patients have been treated in the clinical trial in Europe, one of which was treated with a fresh product formulation and two of which were treated with a cryopreserved product formulation. Two patients have been treated in a compassionate use program in Europe, one with a fresh product formulation and the other with a cryopreserved product formulation. In the future, we expect to treat additional patients in this trial with a cryopreserved formulation of OTL-102. Patients enrolled in these trials have advanced and severe stages of X-CGD.

The primary goals of these clinical trials are to assess safety and efficacy, as measured by biochemical and functional reconstitution through increased nicotinamide adenine dinucleotide phosphate-oxidase, or NADPH, activity in progeny of engrafted cells and stability at 12 months post-treatment.

In these clinical trials, the production of NADPH activity in neutrophils, a biomarker that demonstrates restored granulocyte function, has been measured in patients for up to 24 months post-treatment. As of July 2018, preliminary combined data from the U.S. and U.K. studies, including the compassionate use patients, showed NADPH activity, as measured by dihydrorhodamine, or DHR, assay, above 10% in six patients with at least six months follow-up. Based on the investigator’s review of the scientific literature, they determined that 10% was a clinically meaningful percentage for fighting infections successfully. The graphic below illustrates sustained NADPH levels, as measured for up to 24 months post-treatment.



(1) Excludes data from one patient treated with drug product deemed by the investigator to be a different from OTL-102 drug product.
 † Patient deceased from advanced disease.

As of July 2018, the date of the most recent safety data available to us, safety data from the U.S. patients treated in this clinical trial indicate OTL-102 was generally well-tolerated, with no instances of insertional mutagenesis up to eight months post-treatment. There were eight SAEs reported, none of which were assessed by the investigator as being possibly related to drug product. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All AEs and SAEs resolved with standard of care treatment.

Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR. In the U.K. study, eight SAEs were also reported, one of which was deemed as possibly related to the product. This event is still under investigation by the data safety monitoring board.

Two of the nine patients treated with OTL-102 in these clinical trials died during the three months period following treatment as a result of pre-existing disease-related complications

present at the time of treatment with OTL-102. One patient from the U.K. trial died of acute respiratory distress syndrome. This subject had a pre-existing lung condition. One patient from the U.S. trial developed platelet antibodies due to sensitization after several granulocytes infusions the patient received prior to gene therapy. As a result, following gene therapy he was unable to respond to platelet transfusion and died from hemorrhage. Following this event, in September 2017, the investigators put this trial on hold, and after discussions with the FDA and the data safety monitoring board, the trial was re-initiated in February 2018. The learnings from this patient resulted in a protocol amendment to prevent patients with existing platelet antibodies from enrolling in the trial. Neither of these two fatalities was deemed by the investigator to be related to the therapy. A third fatality was reported involving a patient treated under the compassionate use program at GOSH. Because of this patient's advanced disease stage at the time of enrollment, the patient required a surgical procedure following treatment and died as a result of complications from this procedure. This fatality was deemed by the investigator not to be related to the product. This patient was treated with drug product manufactured under a different manufacturing process than that used for OTL-102, which was deemed by the investigator to be a different drug product than OTL-102, and therefore, this patient's data have been excluded from the data set in these clinical trials.

Gene therapy for treatment of TDBT

Disease overview

Beta-thalassemia is an inherited blood disorder caused by one of over 200 mutations in the hemoglobin beta, or HBB, gene. Patients with beta-thalassemia have low levels of hemoglobin, a protein in red blood cells that carries oxygen to cells throughout the body. TDBT is the most severe form of beta-thalassemia, and requires patients to receive eight or more blood transfusions per year, with the number of transfusions dependent upon the severity of the patient's disease. Symptoms in TDBT patients appear within the first two years of life and include failure to thrive, persistent infections and life-threatening anaemia. Patients with TDBT also suffer from other symptoms such as liver and spleen enlargement, bone deformities and osteopenia, and hypermetabolic state, resulting in chronic malnourishment. Patients often need a multidisciplinary team of cardiologist, hepatologist, endocrinologist, orthopedic, and psychologist support. In the absence of regular blood transfusions, TDBT is usually fatal in infancy.

TDBT is one of the most common genetic diseases, with a global incidence estimated at approximately 25,000 symptomatic individuals born each year.

Limitations of current therapies

The symptoms experienced by most patients with TDBT are severe and often require frequent, life-long blood transfusions to replenish the patient's hemoglobin level. Because iron cannot be excreted by the body, these frequent blood transfusions can cause iron to accumulate in various organs, leading to risk of heart or liver failure. Therefore, patients who receive ongoing blood transfusions must also receive iron chelation therapy to remove the excess iron. These medicines also have side effects and can negatively impact a patient's quality of life. Although HSCT is potentially curative in patients with TDBT, this approach can be associated with significant risks, especially when perfectly-matched cell donors are not available.

Our solution, OTL-300 for treatment of TDBT

We are developing OTL-300 as an autologous *ex vivo* gene therapy to sustainably treat patients with TDBT through a single administration. OTL-300 is manufactured from HSCs isolated from the patient's own mobilized peripheral blood, then modified to add a functional HBB gene using a lentiviral vector. The gene-modified cells are infused back into the patient in a single intra-osseous administration following treatment with a myeloablative conditioning regimen. We plan to investigate treatment through an intravenous administration of OTL-300 as part of the clinical development of this product candidate. OTL-300 is designed to significantly reduce or eliminate the need for blood transfusions in patients with TDBT.

As April 2018, OTL-300 has been evaluated in a total of nine patients, the majority of which have a severe genotype of TDBT, including β^0/β^0 , in an ongoing clinical trial at San Raffaele Hospital in Milan, Italy, with follow-up of up to approximately three years. The clinical trials for this program are being conducted under an investigator-sponsored CTA.

We obtained worldwide rights to this program through the GSK Agreement. OTL-300 has received orphan drug designation from the EMA for the treatment of beta-thalassemia major and intermediate. In addition, the EMA has granted Priority Medicines (PRIME) designation to OTL-300.

Ongoing clinical trials (cryopreserved formulation)

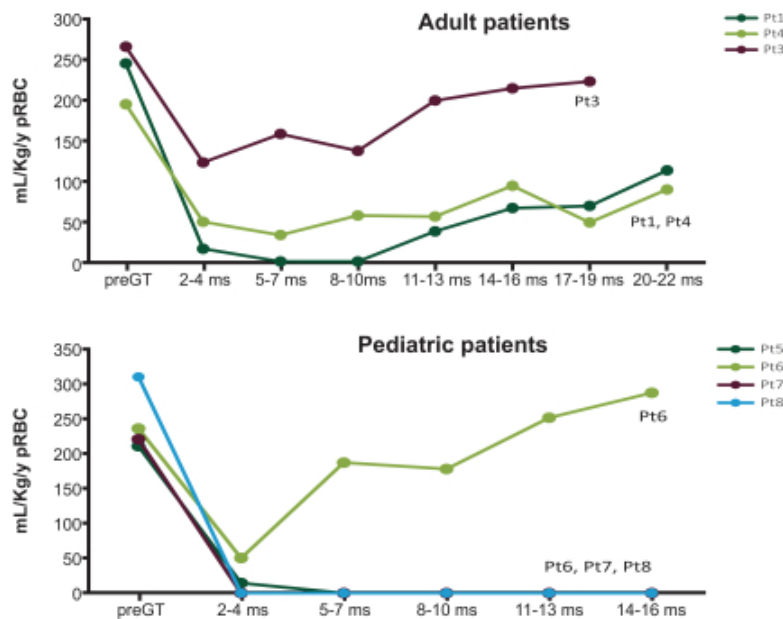
OTL-300 is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The target enrollment in this trial is nine patients with TDBT, and as of September 2018, all nine patients have received a single dose of a cryopreserved formulation of OTL-300. The patients evaluated in this trial include six pediatric patients aged three to 17 years, and three adult patients aged 18 years and over. Following conclusion of this trial at two-years post-treatment, patients will continue to be evaluated in a long-term follow-up clinical trial for an additional six year period.

The primary goals of these clinical trials are to assess the safety and efficacy of a cryopreserved formulation of OTL-300 in TDBT patients, as measured by, for example reduction in required blood transfusions to manage the patients' TDBT and overall survival at 24 months post-treatment.

Of the seven patients with at least 12 months of follow-up as of April 2018, significant reductions in transfusion frequency and volume requirements were observed in five patients, with three of the four pediatric patients being transfusion-free since approximately one month post-treatment. Following treatment, substantial reductions in transfusion volume requirements were observed in two out of three adult patients, with one patient transfusion-free over a period of nine months. The third adult patient at the most recent follow-up showed minimal reduction in transfusion frequency and volume requirements compared to the period before treatment with OTL-300.

The graphs below illustrate the reduction in required blood transfusions for up to 16 and 22 months post-treatment in pediatric and adult patients, respectively.

OTL-300 (TDBT): Blood transfusion requirements before and after treatment



As of April 2018, the date of the most recent safety report available to us, 100% overall survival has been observed, with a follow-up of up to approximately three years. Safety data from the nine patients treated in this clinical trial indicate OTL-300 was generally well-tolerated, with no instances of insertional mutagenesis up to approximately three years post-treatment. There were five SAEs reported, none of which were assessed by the investigator as being related to OTL-300. The SAEs included infection, neutropenia, gastroenteritis, and obstructive pancreatitis. There were no AEs or SAEs leading to the withdrawal of patients from the trial. All SAEs resolved with standard of care treatment. Because follow-up in this clinical trial is ongoing, safety data are preliminary and subject to change. As of the date of this prospectus, we have not been notified by the investigator in this clinical trial of any SUSAR.

Preclinical data for our gene therapy programs

Each of our aforementioned lead programs has been evaluated in preclinical studies of murine models of the target indications. Preclinical development plans have been discussed with or reviewed by the FDA and EMA or E.U. Member State Authorities over the course of drug development interactions or approval of clinical trials.

Our preclinical gene therapy programs for the treatment of MPS-IIIA and MPS-IIIB

Disease overview

MPS-IIIA and MPS-IIIB are life-threatening metabolic diseases that cause accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within one to two years

[Table of Contents](#)

after birth, MPS-IIIA and MPS-IIIB patients experience progressive neurological decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA and MPS-IIIB is between 10 to 25 years and 15 to 30 years, respectively.

The incidence of MPS-IIIA and MPS-IIIB are currently estimated to be one in 100,000 and one in 200,000 live births per year, respectively.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MPS-IIIA and MPS-IIIB. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MPS-IIIA and MPS-IIIB but does not slow or reverse the progression of the underlying disease. HSCT is not considered to be effective treatment options for these diseases. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MPS-IIIA and MPS-IIIB patients, their caregivers and families and healthcare systems.

Our Solution, OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB

We are developing OTL-201 and OTL-202 as autologous *ex vivo* gene therapies for treatment of patients with MPS-IIIA and MPS-IIIB, respectively. In both indications we believe preclinical studies in mice have shown that autologous *ex vivo* gene therapy has the potential to address the neurological manifestations of MPS-IIIA and MPS-IIIB. We plan to submit a CTA with the applicable regulatory authority in Europe for MPS-IIIA by the end of 2019 and plan to continue to progress preclinical development of MPS-IIIB.

We have obtained worldwide development and commercialization rights to OTL-201 for treatment of MPS-IIIA and OTL-202 for treatment of MPS-IIIB from The University of Manchester.

OTL-201 has received orphan drug designation from the EMA and FDA for the treatment of MPS-IIIA and has received rare pediatric disease designation from the FDA.

Preclinical studies

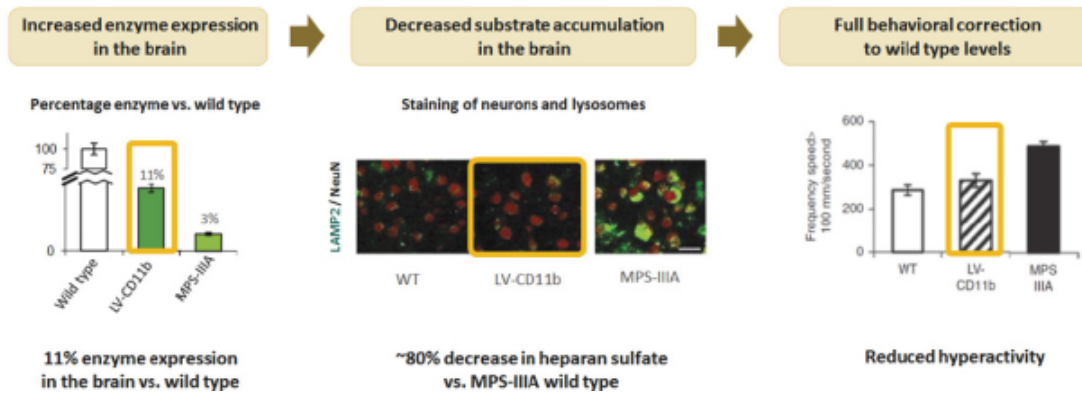
A comprehensive panel of preclinical studies has been performed by The University of Manchester, which we believe supports the use of OTL-201 in clinical trials.

In a mouse model of MPS-IIIA, engraftment of HSCs from a donor mouse modified with GFP using autologous *ex vivo* gene therapy with the selected vector for this program (a hCD11b-coSGSH lentiviral vector) was observed. Sustained gene expression of the GFP-modified HSCs was seen over a follow-up of approximately six months, which we believe supports the stability of the engraftment of modified cells.

Transplantation of gene-modified HSCs resulted in a 4.72-fold increase in enzyme activity relative to wild type enzyme levels and significantly elevated brain enzyme activity. Increased enzyme activity resulted in decreased heparan sulphate substrate accumulation in the brain and correction of behavioral abnormalities, such as hyperactivity and a reduced sense of danger, to normal levels.

Table of Contents

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-III A.



Preclinical studies in a mouse model of MPS-IIIB have demonstrated correction of neurological activity, as measured by reduction in hyperactivity. Lentivirus vector optimization for OTL-202 for treatment of MPS-IIIB is ongoing.

Future applications of our autologous ex vivo gene therapy approach

We believe that our versatile autologous ex vivo gene therapy approach has the potential to deliver promising gene therapies to patients across a broad range of rare diseases. Although our initial focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from ADA-SCID, MLD, WAS, X-CGD and TDBT, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other rare diseases in our target franchise areas, including primary immune deficiencies, neurometabolic disorders and hemoglobinopathies, where ex vivo gene therapy has a comparably high probability of success. For example, we have option rights upon completion of clinical proof of concept studies for MPS-I, CGD and GLD, which would leverage the same autologous ex vivo gene therapy approach.

Our Regulatory Strategy

Due to the nature of our gene therapy product candidates and the indications our product candidates are intended to treat, which are often fatal without treatment, and which are rare or ultra-rare indications, we believe our clinical programs may be eligible to proceed to registration without having to conduct one or more Phase 1 safety studies in healthy volunteers or Phase 3 randomized, double-blind and placebo-controlled clinical trials. Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for the treatment of rare diseases, particularly life threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following one or more clinical trials in a limited patient population, following review of the trial's design, endpoints and clinical data by the applicable regulatory agencies. These determinations are based on the applicable regulatory agency's scientific judgement and these determinations may differ in the United States and the European Union.

For purposes of this prospectus, we refer to an exploratory study, which is sometimes referred to as a Phase 1 or Phase 1/2 clinical trial, as a proof of concept trial, and a confirmatory efficacy and safety study to support submission of a potential marketing application with the applicable regulatory authorities, which is sometimes referred to as a Phase 2/3 or Phase 3 clinical trial or a pivotal trial, as a registrational trial. In some cases applicable regulatory agency may require us to perform analytical studies or conduct additional clinical trials to support analytical comparability of drug product, for example by demonstrating comparability of drug product manufactured using HSCs derived from a patient's mobilized peripheral blood and drug product manufactured using HSCs derived from a patient's bone marrow and/or comparability of drug product that has been cryopreserved and fresh drug product. For purposes of this prospectus we refer to these clinical trials as supportive clinical trials. In addition, certain of our product candidates may be evaluated in clinical trials for which clinical data is not intended to be pooled with data from our registrational trials for purposes of a regulatory submission, but will be submitted to the applicable regulatory agencies for informational purposes. For purposes of this prospectus we refer to these trials as additional clinical trials. In addition, in some cases patients may be ineligible for participation in our clinical trials and may receive treatment under a compassionate use program. We expect that the available safety and efficacy results from all these trials would be included in any regulatory submission we may submit and the applicable regulatory agency with respect to each clinical program the applicable regulatory agency will make a determination as to whether the available data is sufficient to support a regulatory submission. See "Risk factors—The results from our clinical trials for OTL-101 for ADASCID, OTL-200 for MLD, OTL-103 for WAS and for any of our other product candidates may not be sufficiently robust to support the submission of marketing approval for our product candidates," "Risk factors—We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells (HSCs) derived from the patient's mobilized peripheral blood and drug product manufactured using HSCs derived from the patient's bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product," and "Risk factors—To date, most of the clinical trials for our product candidates were conducted as investigator sponsored clinical trials using drug product manufactured at the academic sites."

Manufacturing

The diseases we are targeting affect patients across the world. Therefore, we are implementing our plans to build a commercial-scale manufacturing infrastructure and leverage technologies that will allow us to deliver our gene therapies globally.

Global supply network with experienced CMOs

We currently partner with a network of experienced CMOs, including Oxford BioMedica and MolMed S.p.A., for the supply of our vectors and/or drug product. We have established relationships with commercial CMO partners with the resources and capacity to meet our clinical and existing and expected initial commercial needs. Two of our vector CMOs currently manufacture for approved commercial gene therapy products. Our CMO partners also provide us with access to state-of-the art production technologies, as well as complementary geographic dispersity to mitigate supply chain risk.

Manufacturing efficiencies and scalability

We are in the process of implementing our plans to functionally close and/or automate some process steps for the manufacture of our gene therapies. We currently operate two development laboratory facilities in California and plan to invest in additional facilities to accommodate our expanding technical operations and implement in-house manufacture for some of our CGMP vector and drug product needs. We also continue to invest in the human talent and facility infrastructure required to support the initial development and validation of processes and controls for the manufacture of our product candidates. We believe this industrialization of our manufacturing processes will afford us more flexibility and control over our development programs. We are actively investing in improving the yield of vector and drug product production and enhancing transduction efficiency to lower cost of goods. We are also investigating automation of the entire drug production process. We believe these initiatives will allow us to increase production yield while lowering production costs for our programs.

Cryopreservation of our gene therapy programs

Cryopreservation of the gene-modified cells is a key component of our strategy to deliver potentially transformative gene therapies to patients worldwide. We have developed cryopreserved formulations of our OTL-101, OTL-102, OTL-200 and OTL-300 programs and are in the process of introducing a cryopreserved formulation of our OTL-103 program and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

In the cryopreservation process, a patient's gene-modified HSCs are frozen at extremely low temperatures and then stored to allow quality control testing and release to be performed before introducing the cells back into the patient. Our cryopreserved formulations are expected to have shelf-lives of months to years, enabling us to potentially distribute our products and product candidates from a few centralized manufacturing facilities to geographically dispersed treatment sites. Our ability to ultimately distribute our product candidates globally will facilitate access of the therapies to patients, and reduces the logistical burden on the patients and their families.

Intellectual property and barriers to entry

Our commercial success depends, in part, upon our ability to protect commercially important and proprietary aspects of our business, defend and enforce our intellectual property rights, preserve the confidentiality of our know-how and trade secrets, and operate without infringing misappropriating and otherwise violating valid and enforceable intellectual property rights of others. In particular, we strive to protect the proprietary aspects of our business and to develop barriers to entry that we believe are important to the development and commercialization of our gene therapies. For example, where appropriate, we develop, or acquire exclusive rights to, clinical data for Strimvelis and each of our product candidates, know-how and trade secrets associated with Strimvelis and each of our product candidates. However, we do not own any patents or patent applications that cover Strimvelis or any of our product candidates. We in-license from UCLB and UCLA one family of patent applications directed at OTL-101. We cannot guarantee that patents will issue from any of these patent applications or from any patent

applications we or our licensors may file in the future, nor can we guarantee that any patents that may issue in the future from such patent applications will be commercially useful in protecting Strimvelis or our product candidates. In addition, we plan to rely on regulatory protection based on orphan drug exclusivities, data exclusivities and market exclusivities. See “—Government regulation” for additional information.

We currently rely primarily on know-how and trade secret protection for aspects of our proprietary technologies that we or our licensors believe are not amenable to or appropriate for patent protection, including, for example, clinical data and production information for Strimvelis and each of our product candidates. However, know-how and trade secrets can be difficult to protect. Although we take steps to protect our know-how, trade secrets and other proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or similar know-how, trade secrets or proprietary information or may otherwise gain access to such know-how, trade secrets and other proprietary information or such know-how, trade secrets or other proprietary information may otherwise become known. Moreover, we cannot guarantee that our confidentiality agreements will provide meaningful protection or that they may not be breached and we may not have an adequate remedy for any such breach. As a result, we may be unable to meaningfully protect our know-how, trade secrets and other proprietary information.

In addition, with regard to patent protection, the scope of coverage being sought in a patent application may be reduced significantly before a patent is issued, and even after issuance the scope of coverage may be challenged. As a result, we cannot guarantee that any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

With regards to our OTL-101 product candidate, we have exclusive, worldwide, sub-licensable, licenses pursuant to the UCLB/UCLA Agreement to clinical data and to a patent family containing one pending U.S. patent application with composition of matter claims directed to the OTL-101 product candidate and its use in the treatment of ADA-SCID, and one pending counterpart European patent application. The U.S. patent application, if issued as a U.S. patent, would be expected to expire in 2036, without taking a potential patent term adjustment or extension into account. In addition, under the UCLB/UCLA Agreement, we have non-exclusive, worldwide, sub-licensable, licenses to know-how and materials relating to the OTL-101 product candidate.

With regards to Strimvelis, OTL-103, OTL-200 and OTL-300, and as discussed in detail in “—License agreements”, we have exclusive, worldwide, sub-licensable licenses pursuant to the GSK Agreement and the R&D Agreement to anonymized patient-level data arising from the clinical trials of Strimvelis, OTL-103, OTL-200 and OTL-300 and know-how, including other clinical data and production information relating to Strimvelis, OTL-103, OTL-200, and OTL-300.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment, which provides additional term caused by administrative delays at the USPTO in

granting a patent, or may be shortened if a patent is terminally disclaimed over another patent with an earlier expiration date.

Furthermore, in the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Amendments as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. In the future, if we obtain an issued U.S. patent covering one of our present or future product candidates, and if such product candidate receives FDA approval, we expect to apply for a patent term extension, if available, to extend the term of the patent covering such approved product candidate. We also expect to seek patent term extensions in any jurisdictions where they are available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such an extension should be granted, and even if granted, the length of such an extension.

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, GSK novated to us their R&D Agreement with Telethon-OSR, which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Milan, Italy for MPS-I, CGD and GLD.

Under the GSK Agreement, we are subject to certain obligations to develop and advance certain of the acquired product candidates. For example, we are required to first use best endeavors to file an MAA for OTL-200 for MLD in either Europe or a BLA for MLD in the United States and to subsequently use commercially reasonable efforts to file an MAA or BLA, as applicable, in the other jurisdiction and to market, sell and promote OTL-200 in such jurisdictions. We are also required to use best endeavors to file a BLA for OTL-103 for WAS in the United States and to use commercially reasonable efforts to file an MAA for OTL-103 in Europe, and to subsequently market, sell and promote OTL-103 in such jurisdictions. We are also required to use commercially reasonable efforts to develop and file an MAA or BLA, as applicable, for OTL-300 for TDBT in either the United States or Europe. In addition, we must also use best endeavors to maintain the MAA and regulatory designations for Strimvelis in the European Union and to continue to make Strimvelis available to eligible patients until an alternative gene therapy product has received marketing approval in Europe. We must also continue to make Strimvelis available at the San Raffaele Hospital for as long as a minimum number of patients are treated and entitled to receive reimbursement for the provision of Strimvelis, over a defined period. We intend to continue to make Strimvelis available for so long as we are required to do so under the GSK Agreement.

We are required to use commercially reasonable efforts to obtain a PRV from the FDA for each of Strimvelis, OTL-200, OTL-103 and OTL-300 and to transfer the first such PRV to GSK. GSK also has

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

GSK received a one-time upfront fee of £10.0 million under the GSK Agreement, and we issued to GSK 15,563,230 of our Series B-2 convertible preferred shares and have a payable due to GSK of £4.9 million.

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

We may terminate our development and/or commercialization activities of any of the programs under the GSK Agreement, upon the occurrence of an SAE, or if we believe such program poses a safety risk to patients. GSK may require us to grant a third party a non-exclusive license under the intellectual property we have acquired from GSK under the GSK Agreement if we materially breach of our obligations to use best endeavors and/or commercially reasonable efforts to develop and commercialize the acquired programs and fail to develop and implement a mutually agreeable plan to cure such material breach within a specified time period. The foregoing license only continues until such time as we cure our material breach and we must pay GSK all amounts we receive from the third party in connection with such license.

Telethon-OSR research and development collaboration and license agreement

In April 2018, in connection with our entering into the GSK Agreement, we entered into a deed of novation with GSK, Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, pursuant to which we acquired and assumed all of GSK's rights and obligations under the R&D Agreement with Telethon-OSR for the research, development and commercialization of *ex vivo* HSC gene therapies for ADA-SCID, WAS, MLD, TDBT, X-CGD, MPS-I, and GLD.

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, sublicensable, worldwide license under certain intellectual property rights to develop and commercialize certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD,

[Table of Contents](#)

TDBT, X-CGD, MPS-I and GLD. At the time we entered into the deed of novation agreement, GSK had completed development, launched and commercialized Strimvelis for ADA-SCID in EU, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to the WAS, MLD and TDBT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID, WAS, MLD and TDBT collaboration programs pursuant to the GSK Agreement and to the deed of novation.

Under the R&D Agreement, Telethon-OSR is required to use commercially reasonable efforts to conduct each of the collaboration programs in accordance with development plans approved by a joint steering committee. With respect to those programs in relation to which our option has been exercised, we are required to use commercially reasonable efforts to develop, obtain regulatory approval, launch and promote in both the European Union and the United States all licensed products and to commercialize and manufacture such products at levels sufficient to meet commercial demands. We are required to use best efforts to renew the EU marketing authorization for Strimvelis to enable patients to be treated at the San Raffaele hospital from all referring centers globally, as permitted by applicable law. With certain exceptions, Telethon-OSR is responsible for all costs and activities associated with the collaboration programs prior to our exercise of the option for any such program. We are responsible for the costs and activities associated with the continued development of Strimvelis and each program for which an option under the R&D Agreement is exercised.

As consideration for the licenses and options granted under the R&D Agreement, we are required to make payments to Telethon-OSR upon achievement of certain product development milestones. We are also required to pay Telethon-OSR a fee in connection with the exercise of our option for each collaboration program. We are obligated to pay up to an aggregate of €31M in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDBT programs) and we may become obligated to pay up to an aggregate of €70.5M in connection with option fees and product development milestones with respect to those programs for which we have not to date exercised our exclusive license option under this agreement (that is, for X-CGD, MPS-I and GLD programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves a certain threshold percentage of the market share.

Unless terminated earlier, the R&D Agreement will expire (i) on a product-by-product and country-by-country basis upon the expiration of all payment obligations with respect to such product in such country, (ii) in its entirety upon the expiration of all payment obligations with respect to the last product in all countries in the world and (iii), on a program-by-program basis when no vector or gene therapy product is being researched, developed or commercialized. Either we or Telethon-OSR may terminate the R&D Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time. Additionally, either we or Telethon-OSR may terminate

involvement in a collaboration program for compelling safety reasons, and either we or Telethon-OSR may terminate the R&D Agreement if the other party becomes insolvent. We may also terminate the R&D Agreement either in its entirety or on a program-by-program basis for any reason upon notice to Telethon-OSR.

UCLB/UCLA License Agreement

In February 2016, we entered into a license agreement, or the UCLB/UCLA Agreement, with UCLB and UCLA, pursuant to which we obtained an exclusive, worldwide, sublicenseable license to certain technology, clinical data, manufacturing know-how, and intellectual property rights related to the production of virally transduced HSCs for treatment of patients with ADA-SCID, in addition to certain other rare disease indications. We must use diligent efforts to develop and commercialize a gene therapy product in each of the foregoing indications in the United States, United Kingdom and at least one of France, Germany, Italy and Spain as soon as reasonably possible.

UCLB received an aggregate upfront fee of £1,400,000 and a patent reimbursement fee of £12,524.10 under the UCLB/UCLA Agreement, and we issued to UCLB 4,300,000 and 1,529,545 of our ordinary shares in 2016 and 2017, respectively, and not reflecting the 1-for-0.8003 reverse share split. We are also required to make certain annual administration payments to UCLB upon our receipt of VAT invoices.

Under the UCLB/UCLA Agreement, we are also obligated to pay UCL royalties ranging from low to mid-single-digit percentages on net sales of each of the product candidates subject to the UCLB/UCLA Agreement that receive marketing approval. Our royalty obligations under the UCLB/UCLA Agreement terminate in February 2041. In addition, we are required to pay to UCLB milestone payments up to an aggregate of £28.85 million upon achievement of our first, second and third marketing approvals of product candidates under the UCLB/UCLA Agreement.

Unless terminated earlier, the UCLB/UCLA Agreement will expire in February 2041. We may terminate the UCLB/UCLA Agreement in its entirety or with respect to either UCLB or UCLA for any reason upon prior written notice. Additionally, either we or UCLB may terminate the UCLB/UCLA Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time, or if the other party becomes insolvent.

Oxford BioMedica License and Development Agreement

In November 2016, we entered into a license and development agreement, or the Oxford Development Agreement, with Oxford BioMedica (UK) Limited, or Oxford BioMedica, for the development of gene therapies for ADA-SCID, MPS-IIIa and certain other diseases that we may request be included under the Oxford Development Agreement, such other diseases referred to as Subsequent Indications. The Oxford Development Agreement was amended in June 2017, May 2018, July 2018 and September 2018.

Pursuant to the Oxford Development Agreement, Oxford BioMedica granted us an exclusive, worldwide license under certain intellectual property rights for the purposes of research, development and commercialization of *ex vivo* gene therapy products for the treatment of ADA-SCID, MPS-IIIa and Subsequent Indications, except that such license is non-exclusive to the extent the treatment of a Subsequent Indication is the subject of a certain previous license granted by Oxford BioMedica. Oxford BioMedica also granted us a non-exclusive, worldwide license under

certain intellectual property rights for the purposes of research, development, commercialization and manufacture of *ex vivo* gene therapy products for the treatment of certain diseases other than ADA-SCID, MPS-III A and Subsequent Indications. Under the Oxford Development Agreement, Oxford BioMedica is required to use commercially reasonable efforts to perform the activities set forth in a collaboration plan approved by a joint steering committee, and we are responsible for certain costs of the activities set forth in such collaboration plan.

As consideration for the licenses granted under the agreement, we issued 735,000 of our ordinary shares to Oxford BioMedica, not reflecting the 1-for-0.8003 reverse share split. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 188,462 ordinary shares upon the achievement of the first milestone in November 2017 and 188,462 ordinary shares were issued upon the achievement of further milestones in August 2018, in each instance, not reflecting the 1-for-0.8003 reverse share split. We will be required to issue additional ordinary shares to Oxford BioMedica upon achievement of the remaining milestone under the Oxford Development Agreement. Additionally, we are obligated to pay low single-digit royalties on net sales of licensed products until January 31, 2039. The foregoing royalties are reduced by a mid-double digit percentage in the case of compassionate use of a licensed product in a country until the first commercial sale following marketing authorization in such country. We are also required to pay a set monthly fee to Oxford BioMedica in the event we use a certain Oxford BioMedica system for generating stable cell lines.

Unless terminated earlier, the Oxford Development Agreement will expire when no further payments are due to Oxford BioMedica. We may terminate the performance of the collaboration plan upon notice to Oxford BioMedica, and either party may terminate the performance of the collaboration plan or the Oxford Development Agreement if the other party commits a material breach that is not cured within a certain period of time. Either party may also terminate the Oxford Development Agreement in the event the other party becomes insolvent.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. While we believe that our portfolio of product candidates and scientific expertise in gene therapy provides us with competitive advantages, we face potential competition from many different sources.

We face competition not only from gene therapy companies, but also from companies that are developing novel, non-gene therapy approaches or improving existing treatment approaches. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, if approved.

We are currently aware of the following competitive approaches:

- **ADA-SCID:** The current standards of care for the treatment of ADA-SCID are HSCT and chronic ERT. Adagen, marketed by Leadiant Biosciences, is the only approved ERT for ADA-SCID. We are aware that Leadiant Biosciences has filed a supplemental BLA for elapegedemase, a pegylated recombinant version of Adagen, for the treatment of ADA-SCID.
- **MLD:** There is currently no effective treatment option for patients with MLD. HSCT has demonstrated limited efficacy in arresting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. We are aware that the Institut National de la Santé Et de la Recherche Médicale and Bicêtre hospital in Paris are investigating intracerebral gene therapy for MLD using an

adenovirus AAV-10 vector in a clinical trial. We are also aware that Shire is investigating ERT for MLD with a biweekly intrathecal infusion. We are also aware that Shenzhen University is evaluating a lentiviral *ex vivo* gene therapy for MLD.

- **WAS:** The current standard of care for WAS is HSCT. Patients who are unable to match with a blood donor or who are otherwise ineligible for HSCT may pursue palliative care options, including intravenous immunoglobulin and antimicrobials to prevent and treat infections, topical corticosteroids to manage outbreaks of eczema, platelet transfusions to treat severe bleeds, and immunosuppressive drugs, such as rituximab, to counter autoimmune manifestations. Splenectomy may also be used to treat thrombocytopenia. These palliative approaches do not slow disease progression or address the underlying etiology of WAS. We are also aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with autologous *ex vivo* lentiviral gene therapy. We do not currently have a license or an option to acquire a license from Généthon to these clinical trials in WAS and accordingly Généthon or its licensee may elect to compete against us with respect to this program. To our knowledge no other gene therapy approaches are being currently investigated in WAS.
- **X-CGD:** Management options for patients with X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are aware that Généthon is sponsoring a clinical trial for X-CGD with an autologous *ex vivo* lentiviral gene therapy in France. We are party to an exclusive option and license agreement with Généthon, pursuant to which we have the right to exercise an option with respect to this ongoing clinical trial, which option expires in June 2019. In the event we elect not to exercise this option, Généthon or its licensee may elect to pursue a competitive program in X-CGD using any intellectual property or clinical data derived from this ongoing clinical trial.
- **TDBT:** The current standard of care for the treatment of TDBT involves chronic blood transfusions to address anemia combined with iron chelation therapy to manage the iron overload often associated with such chronic blood transfusions. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. TDBT is a highly competitive research area with several novel approaches under investigation. We are aware that bluebird bio is investigating LentiGlobin, an autologous *ex vivo* gene therapy, for treatment of TDBT and sickle cell disease. In October 2018, bluebird bio announced that the EMA had accepted its MAA for Lentiglobin for the treatment of adolescents and adults with TDBT and a non- β^0/β^0 genotype. bluebird bio has publicly announced its intention to file a BLA in the United States for Lentiglobin in the future. In addition, Memorial Sloane Kettering Cancer Center has been conducting a clinical trial utilizing a lentiviral vector. In addition, we are aware that Sangamo is investigating zinc finger nuclease-mediated gene-correction techniques in TDBT. Several other groups are developing gene editing approaches for beta-thalassemia, including CRISPR Therapeutics, EDITAS and Intellia Therapeutics. CRISPR Therapeutics' CTA for its gene editing approach for beta-thalassemia was approved in 2018. Several other non-gene therapy approaches are under investigation to improve treatment outcomes in beta-thalassemia.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being

concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the research, development, clinical trial, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Each clinical trial protocol for a gene therapy product must be reviewed by the FDA, and, in some instances, the NIH, through its RAC. FDA approval must be obtained before the marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the CBER regulates gene therapy products. The CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in IND for gene therapies. In July 2018, FDA issued draft guidance documents for public comment involving various aspects of gene therapy product development, review, and approval. If finalized by FDA, these guidance documents would represent FDA's current thinking on the development of gene therapy products for specific disease categories, including for rare diseases, as well as update and replace FDA's previous guidance on manufacturing issues related to gene therapy products and long-term follow-up observational studies for gene therapy products.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional laws and regulations restricting or prohibiting the processes we may use. Federal and state legislatures, agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive laws and regulations or interpretations of existing laws or regulations, or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological products development process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an independent IRB or ethics committee at each clinical trial site before each study may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as GCPs and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with CGMP to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or CGTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product biological characteristics, chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation are submitted to and the study is registered with the NIH Office of Science Policy, or OSP, pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA; however, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations, at one of its quarterly public meetings. The OSP will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy

protocol. RAC proceedings and reports are posted to the OSP web site and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. An IND is a request for authorization from the FDA to ship an unapproved, investigational product in interstate commerce and to administer it to humans, and must become effective before clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical trials due to, among other considerations, unreasonable or significant safety concerns, inability to assess safety concerns, lack of qualified investigators, a misleading or materially incomplete investigator brochure, study design deficiencies, interference with the conduct or completion of an a study designed to be adequate and well-controlled for the same or another investigational drug, insufficient quantities of investigational product, lack of effectiveness, or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues or circumstances will not arise that delay, suspend or terminate such studies.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial and its related documentation must be reviewed and approved by an IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Clinical research involving recombinant DNA that is subject to NIH guidelines also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

In August 2018, the NIH published a notice in the Federal Register to seek public comment on its proposal to amend the NIH Guidelines to streamline oversight for human gene transfer clinical

[Table of Contents](#)

research protocols and reduce duplicative reporting requirements while focusing the NIH Guidelines more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The notice included proposed amendments to eliminate RAC review and reporting requirements to NIH for human gene transfer research protocols and to modify the roles and responsibilities of investigators, institutions, IBCs, the RAC, and the NIH to be consistent with these goals.

Clinical trials typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1.* The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2.* The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *Phase 3.* Clinical trials are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for treatment of rare diseases, particularly life threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following a single clinical trial in a limited patient population, sometimes referred to as a Phase 1/2 trial, but which may be deemed a pivotal or registrational trial following review of the trial's design and primary endpoints by the applicable regulatory agencies. Determination of the requirements to be deemed a pivotal or registrational trial is subject to the applicable regulatory authority's scientific judgement and these requirements may differ in the U.S. and the European Union.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical

trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with CGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

After the completion of clinical trials of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the FDA accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. In most cases, the submission of a BLA is subject to a substantial application user fee, although the fee may be waived under certain circumstances. Under the performance goals and policies implemented by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA targets ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates,

and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a “filing” decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with CGMP to assure and preserve the product’s identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult or novel questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a REM is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. To assure CGMP, CGTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a novel product (e.g., new active ingredient, new indication, etc.) must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data

obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the FDA decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, including to subpopulations of patients, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings precautions or interactions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the FDA's breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, the FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Under priority review, the FDA's goal is to review an application in six months once it is filed, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

RMAT designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of RMAT, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. RMAT do not include

those HCT/Ps regulated solely under section 361 of the PHS Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like some of FDA's other expedited development programs, RMAT designation does not change the standards for approval but may help expedite the development or approval process.

Post-approval requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to CGMP. We currently rely, and may continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the CGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of CGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to

comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with CGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain CGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

[Table of Contents](#)

The ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four and 12 year exclusivity periods from the time of first licensure of the product. FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the "first licensure" of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Additional regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Government regulation outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products as well as authorization and approval of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted for each clinical trial to each country's national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country's requirements, the corresponding clinical trial may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Regulation in the European Union

In the European Union, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the European Union and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to regenerate, repair or replace a human tissue. We anticipate that our gene therapy development products would be regulated as ATMPs in the European Union.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit an MAA. The application used to submit the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar

application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five (5) in ten thousand (10,000) persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Pediatric development

In the European Union, companies developing a new medicinal product must agree upon a Pediatric Investigation Plan, or PIP, with the EMA, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-approval controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Other healthcare laws and compliance requirements

In addition to FDA restrictions on the marketing of pharmaceutical products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our business or financial arrangements and relationships through which we market, sell and distribute the gene therapies for which we obtain approval. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback,

[Table of Contents](#)

bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;

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

chiropractors) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;

- federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs; and
- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.

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

Because of the breadth of these laws and the narrowness of the statutory exceptions and safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws.

Violations of fraud and abuse laws may be punishable by criminal and/or civil sanctions, including penalties, fines, imprisonment and/or exclusion or suspension from federal and state healthcare programs such as Medicare and Medicaid and debarment from contracting with the U.S. government. In addition, private individuals have the ability to bring actions on behalf of the U.S. government under the federal False Claims Act as well as under the false claims laws of several states.

Law enforcement authorities are increasingly focused on enforcing fraud and abuse laws, and it is possible that some of our practices may be challenged under these laws. Efforts to ensure that our current and future business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations will involve substantial costs. If our operations, including our arrangements with physicians and other healthcare providers, some of whom receive stock options as compensation for services provided, are found to be in violation of any of such laws or any other governmental regulations that apply to us, we may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, contractual damages, reputational harm, diminished profits and future earnings, the curtailment or restructuring of our operations, exclusion from participation in federal and state healthcare programs (such as Medicare and Medicaid), and imprisonment, any of which could adversely affect our ability to operate our business and our financial results. In addition, our gene therapy program, Strimvelis, was approved by the EMA in 2016, and the

approval and commercialization of Strimvelis subjects us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws. The approval and commercialization of any of our other gene therapies outside the United States will also likely subject us to foreign equivalents of the healthcare laws mentioned above, among other foreign laws.

If any of the physicians or other healthcare providers or entities with whom we expect to do business are found to be not in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs, which may also adversely affect our business.

The risk of our being found in violation of these laws is increased by the fact that many of these laws have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain a robust system to comply with multiple jurisdictions with different compliance and reporting requirements increases the possibility that a healthcare company may violate one or more of the requirements. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial cost.

Healthcare reform

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the ACA was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to new annual, nondeductible fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; expanded healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance; expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; expanded the entities eligible for discounts under the PHS Act's pharmaceutical pricing program, also known as the 340B Drug Pricing Program; created new requirements to report financial arrangements with physicians and teaching hospitals, commonly referred to as the Physician Payments Sunshine Act; created a new requirement to annually report the identity and quantity of drug samples that manufacturers and authorized distributors of record provide to physicians; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established the Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

[Table of Contents](#)

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 payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate.

As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payer separately and will be a time-consuming process.

Payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain and maintain coverage and reimbursement for any product, we may need to conduct expensive clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees

As of June 30, 2018, we had 100 full-time employees, 13 of whom have Ph.D. or M.D. degrees. Of these full-time employees, 70 employees are engaged in research and development activities and 30 employees are engaged in finance, legal, human resources, facilities and general management. We have no collective bargaining agreements with our employees and we have not experienced any work stoppages. We consider our relationship with our employees to be good.

Facilities

Our principal office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom. We lease approximately 9,626 square feet of office space at this location and our lease for this location extends through January 2023. We also lease approximately 5,981 square feet of office space in Boston, Massachusetts, 14,138 square feet of research and development laboratories and office space in Menlo Park, California, and 4,472 square feet of research and development laboratories and office space in Foster City, California. We believe that suitable additional or substitute space will be available as needed to accommodate any future expansion of our operations.

Legal proceedings

From time to time, we may be a party to litigation or subject to claims incident to the ordinary course of business. Although the results of litigation and claims cannot be predicted with certainty, we currently believe that the final outcome of these ordinary course matters will not have a material adverse effect on our business. Regardless of the outcome, litigation can have an adverse impact on us because of defense and settlement costs, diversion of management resources and other factors. We are not currently a party to any material legal proceedings.

Management

Executive officers and directors

The following table sets forth the name, age and position our executive officers and directors as of September 30, 2018.

Name	Age	Position(s)
Executive Officers:		
Mark Rothera	56	President, Chief Executive Officer and Director
Frank E. Thomas	48	Chief Financial Officer and Chief Business Officer
Bobby Gaspar, M.D., Ph.D.	54	Chief Scientific Officer and Director
Non-Executive Directors:		
James A. Geraghty	63	Chairman of the Board of Directors
Joanne T. Beck, Ph.D.	57	Director
Marc Dunoyer	65	Director
Jon Ellis, Ph.D.	51	Director
Alex Pasteur, Ph.D.(1)	47	Director
Charles A. Rowland, Jr.	60	Director
Hong Fang Song	53	Director
Elise Wang(2)	59	Director

(1) Dr. Pasteur has indicated to us his intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

(2) Ms. Wang has indicated to us her intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Executive officers

Mark Rothera has served as our President, Chief Executive Officer and a member of our board of directors since August 2017. Previously, from April 2013 to August 2017, Mr. Rothera served as the Chief Commercial Officer of PTC Therapeutics, Inc., a public biopharmaceutical company. Prior to joining PTC Therapeutics, Inc., Mr. Rothera served as Global President of Aegerion Pharmaceuticals, Inc., a biopharmaceutical company, from April 2012 to January 2013. From January 2006 to March 2012, he served as Vice President and General Manager for the commercial operations of Shire Human Genetic Therapies, Inc. in Europe, the Middle East & Africa. Prior to joining Shire, Mr. Rothera served as Area VP Europe, Middle East and Africa for Chiron BioPharmaceuticals from September 2000 to April 2005. Prior to Chiron, Mr. Rothera held various global strategic and operational marketing and sales roles with French and UK operations of Glaxo Wellcome. Mr. Rothera holds an M.A. in Natural Science from Cambridge University, an M.B.A. from the European Institute for Business Administration and a Diploma in Company Direction from Institute of Directors, United Kingdom. We believe Mr. Rothera is qualified to serve on our board because of his executive experience in our industry.

Frank E. Thomas has served as our Chief Financial Officer and Chief Business Officer since January 2018. Previously, Mr. Thomas served as President and Chief Operating Officer of AMAG Pharmaceuticals, Inc., a publicly traded, specialty pharmaceutical company, from April 2015 to April 2017, as AMAG's Executive Vice President and Chief Operating Officer from May 2012 through April 2015 and as Executive Vice President, Chief Financial Officer and Treasurer from August 2011 through May 2012. Prior to AMAG, he served as Senior Vice President, Chief Operating Officer and Chief Financial Officer for Molecular Biometrics, Inc., a commercial stage

medical diagnostics company, from October 2008 to July 2011. Prior to Molecular Biometrics, Mr. Thomas spent four years at Critical Therapeutics, Inc., a public biopharmaceutical company, from April 2004 to March 2008, where he was promoted to President in June 2006 and Chief Executive Officer in December 2006 from the position of Senior Vice President and Chief Financial Officer. He also served on the Board of Directors of Critical Therapeutics from 2006 to 2008. Prior to 2004, Mr. Thomas served as the Chief Financial Officer and Vice President of Finance and Investor Relations at Esperion Therapeutics, Inc., a public biopharmaceutical company. Since June 2014, Mr. Thomas has served on the board of directors of Zafgen, Inc., a publicly traded biopharmaceutical company. Since July 2017, Mr. Thomas has served on the Board of Directors of Spero Therapeutics, Inc., a publicly traded, development-stage biotechnology company. Mr. Thomas was a member of the Board of Directors of the Massachusetts Biotechnology Council from 2007 to 2015. Mr. Thomas holds a B.B.A. from the University of Michigan, Ann Arbor.

Bobby Gaspar, M.D., Ph.D. has served as our Chief Scientific Officer and as a member of our board of directors since February 2016. Dr. Gaspar joined UCL and GOSH with an interest in gene therapy. Since October 2007, he has been professor of pediatrics and immunology at the UCL Institute of Child Health and Honorary Consultant in pediatric immunology at GOSH. Dr. Gaspar holds an M.B. B.S. from Kings College London and a Ph.D. from UCL. We believe Dr. Gaspar is qualified to serve on our board of directors because of his scientific and industry experience in the field in which we operate.

Non-executive directors

James A. Geraghty has been chairman of our board of directors since May 2018. He also serves as chairman of the boards of directors of publicly traded biopharmaceutical companies Idera Pharmaceuticals, Inc., Juniper Pharmaceuticals, Inc., and Pieris Pharmaceuticals, Inc., and as a member of the board of directors of publicly traded AAV gene therapy company Voyager Therapeutics, Inc. and privately held biotechnology company Fulcrum Therapeutics, Inc. He served as an Entrepreneur in Residence at Third Rock Ventures, a venture capital firm, from May 2013 to October 2016. Prior to that, Mr. Geraghty served as Senior Vice President, North America Strategy and Business Development at Sanofi S.A., a publicly traded pharmaceutical company, from February 2011 to October 2013. Earlier, he held many roles at Genzyme Corporation from 1992 to 2011, most recently as Senior Vice President of International Development and an executive officer. While at Genzyme, his roles included President of Genzyme Europe and General Manager of Genzyme's cardiovascular business. He also served as Chairman, President and CEO of GTC Biotherapeutics, Inc. (formerly Genzyme Transgenics), a pharmaceutical company. Mr. Geraghty holds a B.A. in Psychology and English from Georgetown University, an M.S. in Clinical Psychology from the University of Pennsylvania, and a J.D. from Yale Law School. We believe Mr. Geraghty's experience as a senior executive and service on the boards of other life sciences companies qualifies him to serve on our board of directors.

Joanne T. Beck, Ph.D. has been a member of our board of directors since July 2018. Since April 2016, Dr. Beck has served as the Executive Vice President, Pharmaceutical Development & Operations at Celgene. Prior to joining Celgene, Dr. Beck was the Senior Vice President, Pharmaceutical Development at Shire from January 2012 to April 2016. From May 2004 to January 2012, Dr. Beck held leadership roles in both Pharmaceutical and Vascular Operations at Abbott, most recently as Head of Global Business Excellence and Strategic Program Management. Earlier in her career she had technical leadership roles at Amgen and Genentech. Dr. Beck holds a B.A. in Chemistry from Lewis and Clark College and a Ph.D. in Biochemistry and Molecular

[Table of Contents](#)

Biology from Oregon Health and Science University. We believe Dr. Beck is qualified to serve on our board because of her executive experience in our industry.

Marc Dunoyer has been a member of our board of directors since May 2018. Since November 2013, Mr. Dunoyer has served as the chief financial officer at AstraZeneca plc, a publicly traded pharmaceutical company. At AstraZeneca, Mr. Dunoyer also held the role of Executive Vice President, Global Portfolio & Product Strategy from June 2013 to October 2013. Additionally, Mr. Dunoyer serves on the board of directors of AstraZeneca. Prior to joining AstraZeneca, from February 2010 to March 2013, Mr. Dunoyer served as the foundational Global Head of the Rare Diseases Unit at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Mr. Dunoyer also served on the company's corporate executive team and previously held the position of President for Asia-Pacific and Japan. Mr. Dunoyer has previously held international positions in operations and general management at Hoechst Marion Roussel, a wholly owned subsidiary of Sanofi S.A., a publicly traded pharmaceutical company, and holds an M.B.A. degree from the Hautes Etudes Commerciales and a Bachelor of Law degree from Paris University. We believe Mr. Dunoyer is qualified to serve on our board because of his executive experience in our industry.

Jon Ellis, Ph.D. has been a member of our board of directors since July 2018. Since January 2016, Dr. Ellis has served as the Vice President and Head, Science & Technology Licensing Pharmaceuticals R&D at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Dr. Ellis has also held the roles of Vice President & Head of Platforms BD & Academic, Vice President & Head of Platforms BD, Vice President & Head of Biopharmaceuticals BD, as well as the Head of Antibody Engineering and Biopharm Licensing. Prior to joining GSK in 2001, Dr. Ellis worked as a group leader at GlaxoWellcome plc, a former publicly traded pharmaceutical company, from November 1995 to January 2001. Prior to joining GlaxoWellcome in 1995, Dr. Ellis was a Senior Molecular Biologist at Wellcome Foundation Ltd, a former publicly traded pharmaceutical company, from November 1993 to November 1995. Prior to joining Wellcome Foundation in 1993, Dr. Ellis was a staff scientist at Quantum Biosystems Ltd from October 1992 to November 1993. Dr. Ellis holds a B.A. and M.A. from Magdalene College, University of Cambridge, a Ph.D. from the University of Cambridge, and an M.B.A. from Henley Management College. We believe Dr. Ellis is qualified to serve on our board because of his extensive experience in our industry.

Alex Pasteur, Ph.D. has been a member of our board of directors since November 2015. Dr. Pasteur is a London-based partner at F-Prime Capital Partners and has been a partner since January 2015. At F-Prime Capital Partners, Dr. Pasteur also held the role of Principal from October 2012 to December 2014. Additionally, Dr. Pasteur served as our Chief Executive Officer from September 2016 to September 2017. Previously, Dr. Pasteur worked at MVM Life Science Partners LLP in the USA and Europe. Dr. Pasteur holds an M.A. in Natural Sciences and a Ph.D. in Chemistry from Cambridge University. We believe Dr. Pasteur is qualified to serve on our board of directors because of his extensive experience in our industry. Dr. Pasteur has indicated to us his intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Charles A. Rowland, Jr. has been a member of our board of directors since July 2018. From April 2016 to February 2017, Mr. Rowland served as President and Chief Executive Officer of Aurinia Pharmaceuticals Inc., and as a member of the board of directors of Aurinia from July 2014 to February 2017. Mr. Rowland previously served as Vice President and Chief Financial Officer of ViroPharma Incorporated, an international biopharmaceutical company, from October 2008 until it was acquired by Shire plc, in January 2014. Mr. Rowland previously held positions of increasing responsibility at the following companies: Biovail Pharmaceuticals, Inc., Breakaway Technologies, Inc., Endo Pharmaceuticals Inc., Pharmacia Corporation, Novartis AG,

[Table of Contents](#)

and Bristol-Myers Squibb Co. Mr. Rowland has served as a member of the board of directors, chairman of the compensation committee and member of the audit committee of Viking Therapeutics, Inc, since July 2017. Since January 2015, he has served as a member of the board of directors and chairman of the audit committee and compensation committee of Nabriva Therapeutics, AG, based in Dublin, Ireland. Since March 2015, Mr. Rowland has served as a member of the board of directors and chairman of the audit committee and compensation committee of Blueprint Medicines Corporation, a publicly traded biopharmaceutical company. Mr. Rowland served as a member of the board of directors and audit committee of Idenix Pharmaceuticals, Inc., a biopharmaceutical company, from June 2013, until it was acquired by Merck & Co., Inc. in August 2014. Mr. Rowland served as a member of the board of directors and chairman of the audit committee of Vitae Pharmaceuticals, Inc., from September 2014 until it was acquired by Allergan Inc., in September 2016. Mr. Rowland served as a member of the board of directors and chairman of the audit committee of BIND Therapeutics, Inc., from May 2014 to July 2016. Mr. Rowland holds a B.S. in Accounting from Saint Joseph's University and an M.B.A. with a finance concentration from Rutgers University. We believe that Mr. Rowland's extensive professional experience as a chief financial executive in the biotechnology and pharmaceutical industries and his experience serving as a director of various publicly traded biotechnology companies qualifies him to serve as a member of our board of directors.

Hong Fang Song has served as a member of our board of directors since September 2017. Ms. Song is the founder and has been a Senior Partner of ORI Capital since July 2015. Previously, from January 2010 to June 2015, Ms. Song was the Managing Director of the China Healthcare Business Division of Goldman Sachs, a multinational investment bank and financial services company. Ms. Song holds a B.A. in Economics from Fudan University, China and an M.A. in Economics from Claremont Graduate School in the United States. We believe Ms. Song is qualified to serve on our board because of her extensive experience in the healthcare sector.

Elise Wang has been a member of our board of directors since August 2018. Ms. Wang is currently a Principal on the Public Structured Finance group at Deerfield Management Company, L.P., and has been with Deerfield since 2010. Prior to joining Deerfield, from 2001 to 2007, Ms. Wang was a Senior Research Analyst and Managing Director in healthcare primarily covering the biotechnology industry at Citigroup. From 1996 to 2001, Ms. Wang was a Senior Research Analyst and Managing Director at PaineWebber Inc., where she covered biotechnology. Ms. Wang began her career in healthcare in 1987 as a venture capitalist and banker at PaineWebber Inc. and was an officer of PaineWebber Development Corporation, which managed entities invested in biotechnology and high technology companies. Ms. Wang holds an A.B. in Engineering Sciences with a specialty in Biomechanics from Harvard University and an M.B.A. from Harvard Business School. We believe Ms. Wang is qualified to serve on our board because of her executive experience in our industry. Ms. Wang has indicated to us her intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part.

Family relationships

There are no family relationships among any of our executive officers or directors.

Corporate governance practices

We are a "foreign private issuer," as defined by the SEC. As a result, in accordance with Nasdaq listing requirements, we may rely on home country governance requirements and certain

[Table of Contents](#)

exemptions thereunder rather than complying with Nasdaq corporate governance standards. While we voluntarily follow most Nasdaq corporate governance rules, we may choose to take advantage of the following limited exemptions:

- exemption from filing quarterly reports on Form 10-Q containing unaudited financial and other specified information or current reports on Form 8-K upon the occurrence of specified significant events;
- exemption from Section 16 rules requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades in a short period of time, which will provide less data in this regard than shareholders of U.S. companies that are subject to the Exchange Act;
- exemption from the Nasdaq requirement requiring disclosure of any waivers of the Code of Business Conduct and Ethics, or Code of Ethics, for directors and officers;
- exemption from the requirement to obtain shareholder approval for certain issuances of securities, including shareholder approval of share option plans;
- exemption from the requirement that our audit committee have review and oversight over all “related party transactions,” as defined in Item 7.B of Form 20-F;
- exemption from the requirement that our board have a compensation committee that is composed entirely of independent directors with a written charter addressing the committee’s purpose and responsibilities; and
- exemption from the requirement to have independent director oversight of director nominations.

We intend to follow U.K. corporate governance practices in lieu of Nasdaq corporate governance requirements as follows:

- We do not intend to follow Nasdaq Rule 5620(c) regarding quorum requirements applicable to meetings of shareholders. Such quorum requirements are not required under English law. In accordance with generally accepted business practice, our Articles of Association will provide alternative quorum requirements that are generally applicable to meetings of shareholders.
- We do not intend to follow Nasdaq Rule 5605(b)(2), which requires that independent directors regularly meet in executive sessions where only independent directors are present. Our independent directors may choose to meet in executive sessions at their discretion.

Although we may rely on certain home country corporate governance practices, we must comply with Nasdaq’s Notification of Noncompliance requirement (Nasdaq Rule 5625) and the Voting Rights requirement (Nasdaq Rule 5640). Further, we must have an audit committee that satisfies Nasdaq Rule 5605(c)(3), which addresses audit committee responsibilities and authority and requires that the audit committee consist of members who meet the independence requirements of Nasdaq Rule 5605(c)(2)(A)(ii).

Because we are a foreign private issuer, our directors and senior management are not subject to short-swing profit and insider trading reporting obligations under Section 16 of the Exchange Act. They will, however, be subject to the obligations to report changes in share ownership under Section 13 of the Exchange Act and related SEC rules.

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act, the rules adopted by the SEC and Nasdaq listing rules.

Accordingly, our shareholders will not have the same protections afforded to shareholders of companies that are subject to all of the corporate governance requirements of Nasdaq. For an overview of our corporate governance principles, see the section titled “Description of share capital and articles of association—Differences in corporate law.”

Composition of our board of directors

Our board of directors is currently composed of ten members. Dr. Pasteur and Ms. Wang, currently members of our board of directors, have each indicated to us their intention to resign from our board of directors immediately prior to the effectiveness of the registration statement of which this prospectus forms a part. Our board of directors has determined that, of our ten directors, no director other than Mark Rothera, our Chief Executive Officer, and Bobby Gaspar, our Chief Scientific Officer has a relationship that would interfere with the exercise of independent judgment in carrying out the responsibilities of director and that each of these directors is “independent” as that term is defined under Nasdaq rules.

The Articles of Association provide that upon completion of this offering, our board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution. See “Description of share capital and articles of association—Post-IPO articles of association—Board of directors.”

In October 2018, we entered into a director nomination agreement with Glaxo Group Limited, or GSK, pursuant to which we have agreed to nominate and appoint to our board of directors a designee of GSK, initially Jon Ellis, during the period commencing upon the completion of this offering until such time as we obtain marketing approval and commercially launch OTL-200 for MLD. See “Related party transactions—Director nomination agreement.”

Committees of our board of directors

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

Audit committee

The audit committee consists of Charles A. Rowland, Jr., Marc Dunoyer and Jon Ellis, Ph.D., and assists the board of directors in overseeing our accounting and financial reporting processes. Mr. Rowland will serve as chairman of the audit committee. The audit committee consists

[Table of Contents](#)

exclusively of members of our board who are financially literate, and Mr. Rowland is considered an “audit committee financial expert” as defined by applicable SEC rules and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations. Our board has determined that all of the members of the audit committee satisfy the “independence” requirements set forth in Rule 10A-3 under the Exchange Act. The audit committee will be governed by a charter that complies with Nasdaq rules.

The audit committee’s responsibilities will include:

- recommending the appointment of the independent auditor to the general meeting of shareholders;
- the appointment, compensation, retention and oversight of any accounting firm engaged for the purpose of preparing or issuing an audit report or performing other audit services;
- pre-approving the audit services and non-audit services to be provided by our independent auditor before the auditor is engaged to render such services;
- evaluating the independent auditor’s qualifications, performance and independence, and presenting its conclusions to the full board of directors on at least an annual basis;
- reviewing the adequacy of our internal controls with management and any remediation plan associated with any significant control deficiencies or material weaknesses;
- reviewing and discussing with management and our independent registered public accounting firm our financial statements and our financial reporting process; and
- reviewing, approving or ratifying any related party transactions.

Compensation committee

The compensation committee consists of Charles A. Rowland, Jr. and Joanne T. Beck, Ph.D. and Mr. Rowland will serve as chairman of the compensation committee. Under SEC and Nasdaq rules, there are heightened independence standards for members of the compensation committee, including a prohibition against the receipt of any compensation from us other than standard board member fees. Although foreign private issuers are not required to meet this heightened standard, all of our compensation committee members are expected to meet this heightened standard.

The compensation committee’s responsibilities will include:

- identifying, reviewing and proposing policies relevant to the compensation and benefits of our directors and executive officers;
- evaluating each executive officer’s performance in light of such policies and reporting to the board; and
- overseeing and administering our employee share option scheme or equity incentive plans in operation from time to time.

Nominating committee

The nominating committee consists of James Geraghty and Marc Dunoyer and Mr. Geraghty will serve as chairman of the nominating committee.

The nominating committee's responsibilities will include:

- drawing up selection criteria and appointment procedures for directors;
- recommending nominees for election to our board of directors and its corresponding committees;
- assessing the functioning of individual members of our board of directors and executive officers and reporting the results of such assessment to the board of directors; and
- developing corporate governance guidelines.

Code of business conduct and ethics

We have adopted a Code of Ethics, applicable to our and our subsidiaries' employees, independent contractors, senior management and directors, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A current copy of the Code of Ethics is posted on our website, which is located at www.orchard-tx.com. Information contained on, or that can be accessed through, our website does not constitute a part of this prospectus and is not incorporated by reference herein.

Compensation of executive officers and directors

For the year ended December 31, 2016 and 2017, the aggregate compensation accrued or paid to the members of our board of directors and our executive officers for services in all capacities was \$0.6 million and \$5.1 million, respectively.

During and for the years ended December 31, 2016 and 2017, we had no performance based compensation programs or amount set aside or accrued by us to provide pension, retirement or similar benefits to members of our board of directors or executive officers.

Non-executive director compensation

The compensation of our non-executive directors is determined by our board as a whole, based on a review of current practices in other companies.

Equity incentive plans

2016 Employee share option plan with non-employee sub-plan and U.S. sub-plan

2016 Employee Share Option Plan

Our 2016 Plan was adopted by our board of directors on September 14, 2016 and approved by our shareholders on March 29, 2017 and became effective on September 14, 2016. Our 2016 Plan was subsequently amended by our board of directors on February 7, 2018 and May 25, 2018. The 2016 Plan allows for the grant of options to our employees and executive directors. The board of directors has determined not to grant any further awards under the 2016 Plan following completion of this offering.

The 2016 Plan is administered by our board of directors. The board of directors has the authority to take all actions and make all determinations under the 2016 Plan, to interpret the 2016 Plan

[Table of Contents](#)

and award agreements and to adopt, amend and repeal rules for the administration of the 2016 Plan as it deems advisable, subject to certain limitations imposed under the 2016 Plan, and other applicable laws and stock exchange rules. The plan administrator also has the authority to determine which eligible service providers receive awards, grant awards, set the terms and conditions of all awards under the 2016 Plan, including any vesting and vesting acceleration provisions, subject to the conditions and limitations in the 2016 Plan.

The 2016 Plan provides for the grant of options to purchase our ordinary shares in the future upon written exercise notice. All awards under the 2016 Plan will be set forth in an option certificate, which will detail the terms and conditions of the awards, including any exercise conditions and lapse information.

In connection with certain corporate transactions, including a change of control, our board of directors has broad discretion to take action under the 2016 Plan to prevent the dilution or enlargement of intended benefits, or to facilitate the transaction or event. This includes providing for the assumption or substitution of awards by a successor entity. In addition, in the event of a change in control, the board of directors may accelerate the vesting and exercisability of any option in its discretion. The board of directors may also specify a period of up to 90 days following a change in control during which such options must be exercised and, if not so exercised, such options will terminate.

Our board of directors may amend or terminate the 2016 Plan at any time; however, no amendment, other than an amendment that increases the number of shares available under the 2016 Plan, may affect an award outstanding under the 2016 Plan without the consent of the affected participant.

Except as our board of directors may determine or provide in an option certificate, options granted under the 2016 Plan are generally non-transferrable, except by will or the laws of descent and distribution, and are generally exercisable only by the participant. With regard to tax withholding obligations arising in connection with awards under the 2016 Plan, and exercise price obligations arising in connection with the exercise of options under the 2016 Plan, the plan administrator may, in its discretion, accept cash, wire transfer or check, or a net exercise arrangement.

As of September 30, 2018, options to purchase 10,135,454 shares of common stock were outstanding under the 2016 Plan. Our board of directors has determined not to make any further awards under the 2016 Plan following the pricing of this offering.

2016 Non-Employee Sub-Plan

The 2016 Non-Employee Sub-Plan allows for the grant of options to our non-executive directors, consultants, advisers and other non-employee service providers. Except as modified, all provisions of the 2016 Plan are incorporated into the 2016 Non-Employee Sub-Plan and provides for awards to be made on identical terms to awards made under our 2016 Plan.

2016 U.S. Sub-Plan

The 2016 U.S. Sub-Plan allows for the grant of options to an employee, director or consultant who is a U.S. resident or U.S. taxpayer. The 2016 U.S. Sub-Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under

Section 422 of the Code, and options that do not so qualify. Except as modified, all provisions of the 2016 Plan are incorporated into the 2016 U.S. Sub-Plan and provides for awards to be made on identical terms to awards made under our 2016 Plan.

2018 Share Option and Incentive Plan

Our 2018 Plan was adopted by our board of directors in October 2018 and approved by our shareholders in October 2018 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The 2018 Plan will replace the 2016 Plan as our board of directors has determined not to make additional awards under the 2016 Plan following the closing of our initial public offering. The 2018 Plan allows the compensation committee to make equity-based and cash-based incentive awards to our officers, employees, directors and other key persons (including consultants). Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares.

We have initially reserved 4,254,741 ordinary shares, or the Initial Limit, for the issuance of awards under the 2018 Plan. The 2018 Plan provides that the number of shares reserved and available for issuance under the plan will automatically increase each January 1, beginning on January 1, 2019, by 5% of the outstanding number of ordinary shares on the immediately preceding December 31, or such lesser number of shares as determined by our compensation committee, or the Annual Increase. This number is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

The shares we issue under the 2018 Plan will be authorized but unissued shares or shares that we reacquire. The ordinary shares underlying any awards that are forfeited, cancelled, held back upon exercise or settlement of an award to satisfy the exercise price or tax withholding, reacquired by us prior to vesting, satisfied without any issuance of shares, expire or are otherwise terminated (other than by exercise) under the 2018 Plan and the 2016 Plan will be added back to the ordinary shares available for issuance under the 2018 Plan.

The maximum aggregate number of shares that may be issued in the form of incentive share options shall not exceed the Initial Limit cumulatively increased on January 1, 2019 and on each January 1 thereafter by the lesser of the Annual Increase for such year or 4,254,741 ordinary shares.

The 2018 Plan will be administered by our compensation committee. Our compensation committee has full power to select, from among the individuals eligible for awards, the individuals to whom awards will be granted, to make any combination of awards to participants, and to determine the specific terms and conditions of each award, subject to the provisions of the 2018 Plan. Persons eligible to participate in the 2018 Plan will be those full or part-time officers, employees, non-employee directors and other key persons (including consultants) as selected from time to time by our compensation committee in its discretion.

The 2018 Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under Section 422 of the Code, and options that do not so qualify. The option exercise price of each option will be determined by our compensation committee but may not be less than 100% of the fair market value of our ordinary shares on the date of grant. The term of each option will be fixed by our compensation committee and may not exceed 10 years from the date of grant. Our compensation committee will determine at what time or times each option may be exercised.

[Table of Contents](#)

Our compensation committee may award share appreciation rights subject to such conditions and restrictions as it may determine. Share appreciation rights entitle the recipient to ordinary shares, or cash, equal to the value of the appreciation in our share price over the exercise price. The exercise price of each share appreciation right may not be less than 100% of the fair market value of the ordinary shares on the date of grant.

Our compensation committee may award restricted shares and restricted share units to participants subject to such conditions and restrictions as it may determine. These conditions and restrictions may include the achievement of certain performance goals and/or continued employment with us through a specified vesting period. Our compensation committee may also grant ordinary shares that are free from any restrictions under the 2018 Plan. Unrestricted shares may be granted to participants in recognition of past services or other valid consideration and may be issued in lieu of cash compensation due to such participant. Our compensation committee may grant cash bonuses under the 2018 Plan to participants, subject to the achievement of certain performance goals.

The 2018 Plan provides that in the case of, and subject to, the consummation of a “sale event” as defined in the 2018 Plan, all outstanding awards may be assumed, substituted or otherwise continued by the successor entity. To the extent that the successor entity does not assume, substitute or otherwise continue such awards, then (i) all share options and share appreciation rights will automatically become fully exercisable and the restrictions and conditions on all other awards with time-based conditions will automatically be deemed waived, and awards with conditions and restrictions relating to the attainment of performance goals may become vested and non-forfeitable in connection with a sale event in the compensation committee’s discretion and (ii) upon the effectiveness of the sale event, the 2018 Plan and all awards will automatically terminate. In the event of such termination, (i) individuals holding options and share appreciation rights will be permitted to exercise such options and share appreciation rights (to the extent exercisable) prior to the sale event; or (ii) we may make or provide for a cash payment to participants holding options and share appreciation rights equal to the difference between the per share cash consideration payable to shareholders in the sale event and the exercise price of the options or share appreciation rights (to the extent then exercisable).

Our board of directors may amend or discontinue the 2018 Plan and our compensation committee may amend the exercise price of options and amend or cancel outstanding awards for purposes of satisfying changes in law or any other lawful purpose but no such action may adversely affect rights under an award without the holder’s consent. Certain amendments to the 2018 Plan require the approval of our shareholders. No awards may be granted under the 2018 Plan after the date that is 10 years from the date of shareholder approval. No awards under the 2018 Plan have been made prior to the date of this prospectus.

2018 Employee Share Purchase Plan

Our 2018 Employee Share Purchase Plan, or the ESPP, was adopted by our board of directors in October 2018 and approved by our shareholders in October 2018 and will become effective upon the effectiveness of the registration statement of which this prospectus is part. The ESPP is intended to qualify as an “employee share purchase plan” within the meaning of Section 423(b) of the Code. Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares. The ESPP initially reserves and authorizes the issuance of up to a total of 850,948 ordinary shares to

[Table of Contents](#)

participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 1,500,000 shares or (iii) such number of shares as determined by the ESPP administrator. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

All employees who have completed at least 30 days of employment and whose customary employment is for more than 20 hours per week are eligible to participate in the ESPP. However, any employee who owns 5% or more of the total combined voting power or value of all classes of shares is not eligible to purchase shares under the ESPP.

We will make one or more offerings each year to our employees to purchase shares under the ESPP. Unless otherwise determined by our compensation committee, offerings will usually begin on each January 1 and July 1 and will continue for six-month periods, referred to as offering periods. The first offering began on the effective date of the registration statement of which this prospectus is a part. Each eligible employee may elect to participate in any offering by submitting an enrollment form at least 15 business days before the relevant offering date.

Each employee who is a participant in the ESPP may purchase shares by authorizing payroll deductions of up to 15% of his or her base compensation during an offering period. Unless the participating employee has previously withdrawn from the offering, his or her accumulated payroll deductions will be used to purchase shares on the last business day of the offering period at a price equal to 85% of the fair market value of the shares on the first business day or the last business day of the offering period, whichever is lower. Under applicable U.S. tax rules, an employee's right to purchase shares under the ESPP may not accrue at a rate that exceeds \$25,000 worth of ordinary shares, valued at the start of the purchase period, under the ESPP, for each calendar year in the purchase period.

The accumulated payroll deductions of any employee who is not a participant on the last day of an offering period will be refunded. An employee's rights under the ESPP terminate upon voluntary withdrawal from the plan or when the employee ceases employment with us for any reason.

The ESPP may be terminated or amended by our board of directors at any time. An amendment that increases the number of ordinary shares authorized under the ESPP and certain other amendments require the approval of our shareholders.

Employees

As of December 31, 2017, 2016 and 2015, we had 53, 16 and 0 employees, respectively. As of December 31, 2017, 32 of our employees was based outside of the United Kingdom. All of our employees were engaged in either administrative or research and development functions. None of our employees are covered by a collective bargaining agreement.

Insurance and indemnification

To the extent permitted by the Companies Act 2006, we are empowered to indemnify our directors against any liability they incur by reason of their directorship. We maintain directors'

[Table of Contents](#)

and officers' insurance to insure such persons against certain liabilities. We expect to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering.

In addition to such indemnification, we provide our directors and executive officers with directors' and officers' liability insurance.

Insofar as indemnification of liabilities arising under the Securities Act may be permitted to our board of directors, executive officers, or persons controlling us pursuant to the foregoing provisions, we have been informed that, in the opinion of the SEC, such indemnification is against public policy as expressed in the Securities Act and is therefore unenforceable.

Related party transactions

Since September 1, 2015, we have engaged in the following transactions with our directors, executive officers or holders of more than 5% of our outstanding share capital and their affiliates, which we refer to as our related parties. The share and per share numbers set forth below under this “Related party transaction” section have not been adjusted to reflect the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected prior to completion of this offering.

GSK asset purchase and license agreement

On April 11, 2018, we entered the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first approved gene therapy by the EMA, two late-stage clinical gene therapy programs in ongoing registrational studies: OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, under this agreement, GSK novated to us their R&D Agreement with the Telethon-OSR which includes an exclusive option to license three preclinical programs in development at San Raffaele Hospital in Italy for MPS-I, CGD and GLD.

Upon execution of the agreement, we paid GSK a one-time upfront fee of £10.0 million, and we issued GSK 15,563,230 of our Series B-2 convertible preferred shares. Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. We will pay a mid single-digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and our product candidate, OTL-101. We will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, we may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048. See “Business — License agreements — GSK asset purchase and license agreement” for further information regarding the GSK Agreement.

In connection with this agreement, we also entered into (i) a transitional services agreement with GSK on April 11, 2018, pursuant to which GSK has agreed to provide us certain transitional services in connection with the transfer of the assets acquired under the GSK Agreement, and (ii) an inventory sale agreement with GSK on April 11, 2018, pursuant to which GSK agreed to transfer certain inventory related to the assets acquired under the GSK Agreement.

As a result of the GSK Agreement, GSK is currently a greater than 5% beneficial owner of our outstanding ordinary shares.

Director nomination agreement

In October 2018, we entered into a director nomination agreement with Glaxo Group Limited, or GSK, pursuant to which we have agreed to nominate and appoint to our board of directors a

designee of GSK during the period commencing upon the completion of this offering until such time as we obtain marketing approval and commercially launch OTL-200 for MLD.

Subscription of our Series A convertible preferred shares

In February 2016, with subsequent closings in May 2016, July 2016, August 2016, January 2017 and February 2017, we sold an aggregate of 21,000,000 shares of our Series A convertible preferred shares at a purchase price of £1.00 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series A convertible preferred shares by related persons:

Shareholder	Series A convertible preferred shares	Total purchase price
Affiliates of F-Prime Capital(1)	20,000,001	£ 20,000,001

(1) Consists of (i) 10,000,001 shares of Series A convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 10,000,000 shares of Series A convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital is a holder of 5% or more of our outstanding ordinary shares.

Subscription of our Series B convertible preferred shares

In March 2017, with subsequent closings in August 2017, October 2017, December 2017 and January 2018, we sold an aggregate of 21,198,154 shares of our Series B convertible preferred shares at a subscription price of £4.019 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series B convertible preferred shares by related persons:

Shareholder	Series B convertible preferred shares	Total purchase price
Entities affiliated with F-Prime Capital(1)	3,000,000	£ 12,057,000
Scottish Mortgage Investment Trust plc(2)	4,000,000	£ 16,076,000
Mark Rothera(3)	49,763	£ 199,998

(1) Consists of (i) 1,500,000 shares of Series B convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV LP, and (ii) 1,500,000 shares of Series B convertible preferred shares held by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital is a holder of 5% or more of our outstanding ordinary shares.

(2) Scottish Mortgage Investment Trust plc is a holder of 5% or more of our outstanding ordinary shares.

(3) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

Subscription of our Series C convertible preferred shares

In August 2018, we sold an aggregate of 17,421,600 shares of our Series C convertible preferred shares at a purchase price of \$8.61 per share, pursuant to agreements entered into with the investors. The following table summarizes purchases of our Series C convertible preferred shares by related persons:

Shareholder	Series C convertible preferred shares	Total purchase price
Entities affiliated with Deerfield Management Company(1)	5,807,200	\$ 49,999,992
Scottish Mortgage Investment Trust plc(2)	871,080	\$ 7,499,998
Mark Rothera(3)	31,213	\$ 268,796
Frank E. Thomas(4)	11,614	\$ 100,000
James A. Geraghty(5)	42,973	\$ 370,000
Joanne T. Beck, Ph.D.(6)	11,614	\$ 100,000
Marc Dunoyer(7)	46,457	\$ 400,000
Charles A. Rowland, Jr.(8)	11,614	\$ 100,000

(1) Consists of (i) 580,720 shares of Series C convertible preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,613,240 shares of Series C convertible preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,613,240 shares of Series C convertible preferred shares held by Deerfield Private Design Fund IV, L.P. Deerfield Management Company is a holder of 5% or more of our outstanding ordinary shares.

(2) Scottish Mortgage Investment Trust plc is a holder of 5% or more of our outstanding ordinary shares.

(3) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

(4) Mr. Thomas is our Chief Financial Officer and Chief Business Officer.

(5) Mr. Geraghty is the chairman of our board of directors.

(6) Dr. Beck is a member of our board of directors.

(7) Mr. Dunoyer is a member of our board of directors.

(8) Mr. Rowland, Jr. is a member of our board of directors.

Agreements with shareholders

In connection with the subscriptions of our Series A, Series B and Series C convertible preferred shares, we entered into subscription and shareholder agreements containing registration rights and information rights, among other things, with certain holders of our convertible preferred shares. These shareholder agreements will terminate upon the closing of this offering, except for the registration rights granted under our investors' rights agreement, as more fully described in "Description of share capital and articles of association—Registration rights."

Agreements with our executive officers and directors

We have entered into employment agreements with certain of our executive officers and service agreements with our non-executive directors. These agreements contain customary provisions and representations, including confidentiality, non-competition, non-solicitation and inventions assignment undertakings by the executive officers. However, the enforceability of the non-competition provisions may be limited under applicable law.

Indemnification agreements

We intend to enter into a deed of indemnity with each of our directors and executive officers prior to the completion of this offering. These agreements and our Articles of Association require us to indemnify our directors and executive officers to the fullest extent permitted by law.

Related person transaction policy

In connection with this offering, we have adopted a written related party transactions policy that such transactions must be approved by our audit committee. This policy became effective on the date on which the registration statement of which this prospectus is part was declared effective by the SEC. Pursuant to this policy, the audit committee has the primary responsibility for reviewing and approving or disapproving “related person transactions,” which are transactions between us and related persons in which the related person has a direct or indirect material interest. For purposes of this policy, a related person will be defined as a director, executive officer, nominee for director, or greater than 5% beneficial owner of any class of our voting securities, and their immediate family members.

Principal shareholders

The following table sets forth information with respect to the beneficial ownership of Orchard Therapeutics Limited's ordinary shares as of September 30, 2018, after giving effect to our corporate reorganization, for:

- each beneficial owner of 5% or more of our outstanding ordinary shares;
- each of our directors and executive officers; and
- all of our directors and executive officers as a group.

Beneficial ownership is determined in accordance with the rules of the SEC. These rules generally attribute beneficial ownership of securities to persons who possess sole or shared voting power or investment power with respect to those securities and include ordinary shares that can be acquired within 60 days of September 30, 2018. Percentage ownership calculations are based on 69,761,485 ordinary shares outstanding as of September 30, 2018, after giving effect to the conversion of all of our convertible preferred shares into ordinary shares on a one-for-one basis and our corporate reorganization as described elsewhere in this prospectus including the 1-for-0.8003 reverse split to be effected prior to completion of this offering.

The percentage of shares beneficially owned after completion of this offering is based on 84,047,200 ordinary shares outstanding after this offering, including 14,285,715 ordinary shares in the form of ADSs issued in connection with this offering, assuming no exercise of the underwriters' option to purchase additional ADSs.

The following table does not give effect to any ADSs that may be acquired by our directors or executive officers pursuant to our directed share program.

Except as otherwise indicated, all of the shares reflected in the table are ordinary shares and all persons listed below have sole voting and investment power with respect to the shares beneficially owned by them, subject to applicable community property laws. The information is not necessarily indicative of beneficial ownership for any other purpose.

As of September 30, 2018, 35,555,013 ordinary shares, representing 51.0% of our issued and outstanding shares, were held by 34 U.S. shareholders of record.

Except as otherwise indicated in the table below, addresses of the directors, executive officers and named beneficial owners are in care of Orchard Therapeutics Limited, 108 Cannon Street, London EC4N 6EU, United Kingdom.

Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
<i>5% or Greater Shareholders:</i>			
Entities affiliated with F-Prime(1)	20,407,650	29.3%	24.3
GSK(2)	12,455,252	17.9%	14.8
Entities affiliated with Deerfield Management Company(3)	4,647,500	6.7%	5.5
Scottish Mortgage Investment Trust plc(4)	3,898,325	5.6%	4.6
<i>Executive Officers and Directors:</i>			
Mark Rothera(5)	524,090	*	*
Frank E. Thomas(6)	9,254	*	*
Bobby Gaspar, M.D., Ph.D.(7)	831,735	1.2%	1.0
James A. Geraghty(8)	34,391	*	*
Joanne T. Beck, Ph.D.(9)	9,294	*	*

[Table of Contents](#)

Name of beneficial owner	Number of shares beneficially owned	Percentage of shares beneficially owned	
		Before offering	After offering
Marc Dunoyer(10)	37,179	*	*
Jon Ellis, Ph.D.	—	—	—
Alex Pasteur, Ph.D.	—	—	—
Charles A. Rowland, Jr.(11)	9,294	*	*
Hong Fang Song	—	—	—
Elise Wang	—	—	—
All current directors and executive officers as a group (11 persons)(12)	1,455,277	2.1%	1.7%

* Represents beneficial ownership of less than one percent.

- (1) Consists of (i) 1,000,375 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (ii) 8,003,000 of our ordinary shares issuable upon conversion of our Series A convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iii) 1,200,450 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; (iv) 1,000,375 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; (v) 8,003,000 shares of our ordinary shares issuable upon conversion of our Series A convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP; and (vi) 1,200,450 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares held of record by F-Prime Capital Partners Healthcare Fund IV-A LP. F-Prime Capital Partners Healthcare Advisors Fund IV LP is the general partner of F-Prime Capital Partners Healthcare Fund IV LP. F-Prime Capital Partners Healthcare Advisors Fund IV-A LP is the general partner of F-Prime Capital Partners Healthcare Fund IV-A LP. Each of F-Prime Capital Partners Healthcare Advisors Fund IV LP and F-Prime Capital Partners Healthcare Advisors Fund IV-A LP is solely managed by Impresa Management LLC, the managing member of its general partner and investment manager. Each of the entities listed above expressly disclaims beneficial ownership of the securities listed above except to the extent of any pecuniary interest therein. The address of these entities is 245 Summer Street, Boston, MA 02210.
- (2) Consists of 12,445,252 of our ordinary shares issuable upon conversion of our Series B-2 convertible preferred shares held by GSK. The board of directors of GSK may be deemed to share voting and investment authority over the shares held by GSK. The address of GSK is 980 Great West Road, Brentford, Middlesex, London TW8 9GS, UK.
- (3) Consists of (i) 464,750 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Special Situations Fund, L.P.; (ii) 2,091,375 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Private Design Fund III, L.P.; and (iii) 2,091,375 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Deerfield Private Design Fund IV, L.P. Deerfield Mgmt, L.P. is the general partner of Deerfield Special Situations Fund, L.P. Deerfield Mgmt III, L.P. is the general partner of Deerfield Private Design Fund III, L.P. Deerfield Mgmt IV, L.P. is the general partner of Deerfield Private Design Fund IV, L.P. (collectively with Deerfield Special Situations Fund, L.P. and Deerfield Private Design Fund III, L.P., the "Deerfield Funds"). Deerfield Management Company, L.P. is the investment manager of each of the Deerfield Funds. Mr. James E. Flynn is the sole member of the general partner of each of Deerfield Mgmt, L.P., Deerfield Mgmt III, L.P., Deerfield Mgmt IV, L.P. and Deerfield Management Company, L.P. Deerfield Mgmt, L.P. may be deemed to beneficially own the shares held by Deerfield Special Situations Fund, L.P. Deerfield Mgmt III, L.P. may be deemed to beneficially own the shares held by Deerfield Private Design III, L.P. Deerfield Mgmt IV, L.P. may be deemed to beneficially own the shares held by Deerfield Private Design Fund IV, L.P. Each of Deerfield Management Company, L.P. and Mr. James E. Flynn may be deemed to beneficially own the securities held by the Deerfield Funds. The address of the Deerfield Funds is 780 Third Avenue, 37th Floor, New York, NY 10017.
- (4) Consists of (i) 3,201,200 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares and (ii) 697,125 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares held by Scottish Mortgage Investment Trust plc ("SMIT"). As investment manager for SMIT, Baillie Gifford & Co. may be deemed to share voting and investment control over the shares held by SMIT. SMIT is a publicly traded company. The address for SMIT is c/o Baillie Gifford & Co., Calton Square, 1 Greenside Row, Edinburgh EH1 3AN, United Kingdom.
- (5) Consists of (i) 39,825 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares, (ii) 24,979 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares and (iii) 459,286 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.
- (6) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.
- (7) Consists of (i) 417,319 of our ordinary shares and (ii) 414,416 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.
- (8) Consists of 34,391 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.
- (9) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.
- (10) Consists of 37,179 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.
- (11) Consists of 9,294 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares.
- (12) Consists of (i) 417,319 of our ordinary shares, (ii) 39,825 of our ordinary shares issuable upon conversion of our Series B convertible preferred shares, (iii) 124,431 of our ordinary shares issuable upon conversion of our Series C convertible preferred shares and (iv) 873,702 of our ordinary shares issuable upon exercise of options within 60 days of September 30, 2018.

Description of share capital and articles of association

The following describes our issued share capital, summarizes the material provisions of our articles of association and highlights certain differences in corporate law in the United Kingdom and the United States.

We were incorporated pursuant to the laws of England and Wales as Orchard Rx Limited in August 2018 to become a holding company for Orchard Therapeutics Limited. Pursuant to the terms of our corporate reorganization, all of the issued share capital in Orchard Therapeutics Limited were exchanged for identical shares in Orchard Rx Limited and, as a result, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited. On October 29, 2018, Orchard Rx Limited was re-registered as a public limited company and changed its name to Orchard Therapeutics plc. See “Corporate reorganization” for more information.

We are registered with the Registrar of Companies in England and Wales under number 11494381, and our registered office is at 108 Cannon Street, London EC4N 6EU, United Kingdom.

Certain resolutions were passed by our shareholders prior to the completion of this offering. These include resolutions for the:

- adoption of new articles of association that will become effective upon the completion of this offering. See “—Post-IPO articles of association” below;
- general authorization of our directors for purposes of Section 551 of the Companies Act 2006 to issue shares in the company and grant rights to subscribe for or convert any securities into shares in the company up to a maximum aggregate nominal amount of £113,023,851.50 for a period of five years; and
- empowering of our directors pursuant to Section 570 of Companies Act 2006 to issue equity securities for cash pursuant to the Section 551 authority referred to above as if the statutory preemption rights under Section 561(1) of the Companies Act 2006 did not apply to such allotments.

Issued share capital

As of September 30, 2018, and prior to the 1-for-0.8003 reverse split of our ordinary and convertible preferred shares to be effected prior to completion of this offering, the issued share capital of Orchard Therapeutics Limited was 11,986,245 ordinary shares and 75,182,984 convertible preferred shares. The nominal value of our ordinary shares and convertible preferred shares is £0.00001 per share and each issued ordinary share and convertible preferred share is fully paid. The issued share capital consisted of 11,986,245 ordinary shares, 21,000,000 Series A convertible preferred shares, 21,198,154 Series B convertible preferred shares, 15,563,230 Series B-2 convertible preferred shares and 17,421,600 Series C convertible preferred shares. As of September 30, 2018, the issued share capital of Orchard Rx Limited was 1 ordinary share of £0.00001. Following the exchange of shares of Orchard Therapeutics Limited for shares of Orchard Rx Limited, the issued share capital of Orchard Rx Limited is the same number of ordinary and convertible preferred shares in the same classes. As of the completion of the corporate reorganization and this offering, including the 1-for-0.8003 reverse split of our ordinary and convertible preferred shares, our issued share capital will be 84,047,200 ordinary shares.

Ordinary shares

In accordance with our Articles of Association to be in effect upon the completion of this offering, the following summarizes the rights of holders of our ordinary shares:

- each holder of our ordinary shares is entitled to one vote per ordinary share on all matters to be voted on by shareholders generally;
- the holders of the ordinary shares shall be entitled to receive notice of, attend, speak and vote at our general meetings; and
- holders of our ordinary shares are entitled to receive such dividends as are recommended by our directors and declared by our shareholders.

Registered shares

We are required by the Companies Act 2006 to keep a register of our shareholders. Under English law, the ordinary shares are deemed to be issued when the name of the shareholder is entered in our share register. The share register therefore is prima facie evidence of the identity of our shareholders, and the shares that they hold. The share register generally provides limited, or no, information regarding the ultimate beneficial owners of our ordinary shares. Our share register is maintained by our registrar. Holders of our ADSs will not be treated as one of our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see "Description of American depositary shares" in this prospectus.

Under the Companies Act 2006, we must enter an allotment of shares in our share register as soon as practicable and in any event within two months of the allotment. We will perform all procedures necessary to update the share register to reflect the ordinary shares being sold in this offering, including updating the share register with the number of ordinary shares to be issued to the depositary upon the closing of this offering. We also are required by the Companies Act 2006 to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

We, any of our shareholders or any other affected person may apply to the court for rectification of the share register if:

- the name of any person, without sufficient cause, is wrongly entered in or omitted from our register of members; or
- there is a default or unnecessary delay in entering on the register the fact of any person having ceased to be a member or on which we have a lien, provided that such delay does not prevent dealings in the shares taking place on an open and proper basis.

Preemptive rights

English law generally provides shareholders with preemptive rights when new shares are issued for cash; however, it is possible for the articles of association, or shareholders in general meeting, to exclude preemptive rights. Such an exclusion of preemptive rights may be for a maximum

period of up to five years from the date of adoption of the articles of association, if the exclusion is contained in the articles of association, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by our shareholders upon its expiration (i.e., at least every five years). In October 2018, our shareholders approved the exclusion of preemptive rights for a period of five years from the date of approval, which exclusion will need to be renewed upon expiration (i.e., at least every five years) to remain effective, but may be sought more frequently for additional five-year terms (or any shorter period). In October 2018, our shareholders approved the exclusion of preemptive rights for the allotment of ordinary shares in connection with this offering.

Registration rights

Upon the completion of this offering, the holders of 60,168,900 shares of our ordinary shares issuable upon the conversion of our Series A, Series B, Series B-2 and Series C convertible preferred shares, will be entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of an investment and shareholders' agreement between us and holders of our convertible preferred shares. The investment and shareholders' agreement includes demand registration rights, short-form registration rights and piggyback registration rights.

Demand registration rights

Beginning 180 days after the effective date of this registration statement, the holders of 60,168,900 shares of our ordinary shares issuable upon the conversion of convertible preferred shares upon closing of this offering are entitled to demand registration rights. Under the terms of the investment and shareholders' agreement, we will be required, upon the written request of holders of a majority of these securities to file a registration statement and use best efforts to effect the registration of all or a portion of these shares for public resale. We are required to effect only two registrations pursuant to this provision of the investment and shareholders' agreement.

Short-form registration rights

Pursuant to the investment and shareholders' agreement, if we are eligible to file a registration statement on Form F-3 or Form S-3, upon the written request of holders of a majority of these securities at an aggregate offer price of at least \$5.0 million, we will be required to effect a registration of such shares. We are required to effect only two registrations in any twelve month period pursuant to this provision of the investment and shareholders' agreement. The right to have such shares registered on Form F-3 or Form S-3 is further subject to other specified conditions and limitations.

Piggyback registration rights

Pursuant to the investment and shareholders' agreement, if we register any of our securities either for our own account or for the account of other security holders, other than in connection with our initial public offering or a registration for any employee benefit plan, corporate reorganization, or the offer or sale of debt securities, the holders of these shares are entitled to include their shares in the registration. Subject to certain exceptions contained in the investment and shareholders' agreement, we and the underwriters may limit the number of shares included

in the underwritten offering to the number of shares which we and the underwriters determine in our sole discretion will not jeopardize the success of the offering.

Indemnification

Our investors' rights agreement contains customary cross-indemnification provisions, under which we are obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to us, and they are obligated to indemnify us for material misstatements or omissions attributable to them.

Expiration of registration rights

The registration rights granted under the investment and shareholders' agreement will terminate on the earliest of (i) a deemed liquidation event, as defined in our Articles of Association, and (ii) the fifth anniversary of the completion of this offering.

Post-IPO articles of association

Our Articles of Association, or the Articles, were approved by our shareholders prior to the completion of this offering and were adopted with effect from the completion of the offering. A summary of the terms of the Articles is set out below. The summary below is not a complete copy of the terms of the Articles.

The Articles contain no specific restrictions on our purpose and therefore, by virtue of section 31(1) of the Companies Act 2006, our purpose is unrestricted.

The Articles contain, among other things, provisions to the following effect:

Share capital

Our share capital will consist of ordinary shares. We may issue shares with such rights or restrictions as may be determined by ordinary resolution, including shares which are to be redeemed, or are liable to be redeemed at our option or the holder of such shares.

Voting

The shareholders have the right to receive notice of, and to vote at, our general meetings. Each shareholder who is present in person (or, being a corporation, by representative) at a general meeting on a show of hands has one vote and, on a poll, every such holder who is present in person (or, being a corporation, by representative) or by proxy has one vote in respect of every share held by him.

Variation of rights

Whenever our share capital is divided into different classes of shares, the special rights attached to any class may be varied or abrogated either with the consent in writing of the holders of three-fourths in nominal value of the issued shares of that class or with the sanction of a special resolution passed at a general meeting of the holders of the shares of that class and may be so varied and abrogated whilst the company is a going concern.

Dividends

We may, subject to the provisions of the Companies Act 2006 and the Articles, by ordinary resolution from time to time declare dividends to be paid to shareholders not exceeding the amount recommended by our board of directors. Subject to the provisions of the Companies Act 2006, in so far as, in the board of directors' opinions, our profits justify such payments, the board of directors may pay interim dividends on any class of our shares.

Any dividend unclaimed after a period of 12 years from the date such dividend was declared or became payable shall, if the board of directors resolve, be forfeited and shall revert to us. No dividend or other moneys payable on or in respect of a share shall bear interest as against us.

Liquidation Preference

On a distribution of assets on a liquidation, the surplus assets remaining after payment of liabilities shall be distributed among the holders of ordinary shares pro rata to the number of ordinary shares held.

Transfer of ordinary shares

Each member may transfer all or any of his shares which are in certificated form by means of an instrument of transfer in any usual form or in any other form which the board of directors may approve. Each member may transfer all or any of his shares which are in uncertificated form by means of a "relevant system" (i.e., the CREST System) in such manner provided for, and subject as provided in, the CREST Regulations.

The Board may, in its absolute discretion, refuse to register a transfer of certificated shares unless:

- (i) it is for a share which is fully paid up;
- (ii) it is for a share upon which the company has no lien;
- (iii) it is only for one class of share;
- (iv) it is in favor of a single transferee or no more than four joint transferees;
- (v) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the board of directors to be exempt from stamp duty; and
- (vi) it is delivered for registration to the registered office of the company (or such other place as the board of directors may determine), accompanied (except in the case of a transfer by a person to whom the company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the board of directors may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

The board of directors may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the CREST Regulations and the CREST System.

Allotment of shares and preemption rights

Subject to the Companies Act 2006 and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the board of directors may determine (including shares which are to be redeemed, or are liable to be redeemed at the option of the company or the holder of such shares).

In accordance with section 551 of the Companies Act 2006, the board of directors may be generally and unconditionally authorized to exercise all the powers of the company to allot shares up to an aggregate nominal amount equal to the amount stated in the relevant ordinary resolution authorizing such allotment. The authorities referred to above were included in the special resolution passed in October 2018 and remain in force at the date of this prospectus.

The provisions of section 561 of the Companies Act 2006 (which confer on shareholders rights of preemption in respect of the allotment of equity securities which are paid up in cash) apply to the company except to the extent disapplied by special resolution of the company. Such preemption rights have been disapplied pursuant to the special resolution passed in October 2018.

Alteration of share capital

The company may by ordinary resolution consolidate or divide all of its share capital into shares of larger nominal value than its existing shares, or cancel any shares which, at the date of the ordinary resolution, have not been taken or agreed to be taken by any person and diminish the amount of its share capital by the nominal amount of shares so cancelled or sub-divide its shares, or any of them, into shares of smaller nominal value.

The company may, in accordance with the Companies Act 2006, reduce or cancel its share capital or any capital redemption reserve or share premium account in any manner and with and subject to any conditions, authorities and consents required by law.

Board of directors

Unless otherwise determined by the company by ordinary resolution, the number of directors (other than any alternate directors) shall not be less than two, but there shall be no maximum number of directors.

Subject to the Articles and the Companies Act 2006, the company may by ordinary resolution appoint a person who is willing to act as a director and the board of directors shall have power at any time to appoint any person who is willing to act as a director, in both cases either to fill a vacancy or as an addition to the existing board of directors.

The Articles of Association provide that upon completion of this offering, our board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting our entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

[Table of Contents](#)

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution.

Subject to the provisions of the Articles, the board of directors may regulate their proceedings as they deem appropriate. A director may, and the secretary at the request of a director shall, call a meeting of the directors.

The quorum for a meeting of the board of directors shall be fixed from time to time by a decision of the board of directors, but it must never be less than two and unless otherwise fixed, it is two.

Questions and matters requiring resolution arising at a meeting shall be decided by a majority of votes of the participating directors, with each director having one vote. In the case of an equality of votes, the chairman will only have a casting vote or second vote when an acquisition has been completed.

Directors shall be entitled to receive such remuneration as the board shall determine for their services to the company as directors, and for any other service which they undertake for the company provided that the aggregate fees payable to the directors must not exceed £250,000 per annum. The directors shall also be entitled to be paid all reasonable expenses properly incurred by them in connection with their attendance at meetings of shareholders or class meetings, board of director or committee meetings or otherwise in connection with the exercise of their powers and the discharge of their responsibilities in relation to the company.

The board of directors may, in accordance with the requirements in the Articles, authorize any matter proposed to them by any director which would, if not authorized, involve a director breaching his duty under the Companies Act 2006, to avoid conflicts of interests.

A director seeking authorization in respect of such conflict shall declare to the board of directors the nature and extent of his interest in a conflict as soon as is reasonably practicable. The director shall provide the board with such details of the matter as are necessary for the board to decide how to address the conflict together with such additional information as may be requested by the board.

Any authorization by the board of directors will be effective only if:

- (i) to the extent permitted by the Companies Act 2006, the matter in question shall have been proposed by any director for consideration in the same way that any other matter may be proposed to the directors under the provisions of the Articles;
- (ii) any requirement as to the quorum for consideration of the relevant matter is met without counting the conflicted director and any other conflicted director; and
- (iii) the matter is agreed to without the conflicted director voting or would be agreed to if the conflicted director's and any other interested director's vote is not counted.

Subject to the provisions of the Companies Act 2006, every director, secretary or other officer of the company (other than an auditor) is entitled to be indemnified against all costs, charges, losses, damages and liabilities incurred by him in the actual purported exercise or discharge of his duties or exercise of his powers or otherwise in relation to them.

Table of Contents

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 uncertificated share or otherwise to enforce a lien in respect of it.

Other relevant laws and regulations

Mandatory bid

- (i) The Takeover Code will apply to the company for so long as its central management and control is considered to be in the United Kingdom. Under the Takeover Code, where:
- (a) any person, together with persons acting in concert with him, acquires, whether by a series of transactions over a period of time or not, an interest in shares which (taken together with shares in which he is already interested, and in which persons acting in concert with him are interested) carry 30% or more of the voting rights of a company; or
 - (b) any person who, together with persons acting in concert with him, is interested in shares which in the aggregate carry not less than 30% of the voting rights of a company but does not hold shares carrying more than 50% of such voting rights and such person, or any person acting in concert with him, acquires an interest in any other shares which increases the percentage of shares carrying voting rights in which he is interested;

such person shall, except in limited circumstances, be obliged to extend offers, on the basis set out in Rules 9.3, 9.4 and 9.5 of the Takeover Code, to the holders of any class of equity share capital, whether voting or non-voting, and also to the holders of any other class of transferable securities carrying voting rights. Offers for different classes of equity share capital must be comparable; the Takeover Panel should be consulted in advance in such cases.

- (ii) An offer under Rule 9 of the Takeover Code must be in cash and at the highest price paid for any interest in the shares by the person required to make an offer or any person acting in concert with him during the 12 months prior to the announcement of the offer.
- (iii) Under the Takeover Code, a “concert party” arises where persons acting together pursuant to an agreement or understanding (whether formal or informal and whether or not in writing) actively cooperate, through the acquisition by them of an interest in shares in a company, to obtain or consolidate control of the company. “Control” means holding, or aggregate holdings, of an interest in shares carrying 30% or more of the voting rights of the company, irrespective of whether the holding or holdings give *de facto* control.

Squeeze-out

- (i) Under sections 979 to 982 of the Companies Act 2006, if an offeror were to acquire, or unconditionally contract to acquire, not less than 90% of the ordinary shares of the company, it could then compulsorily acquire the remaining 10%. It would do so by sending a notice to outstanding shareholders telling them that it will compulsorily acquire their shares, provided that no such notice may be served after the end of: (a) the period of three months beginning with the day after the last day on which the offer can be accepted; or (b) if earlier, and the offer is not one to which section 943(1) of the Companies Act 2006 applies, the period of six months beginning with the date of the offer.
- (ii) Six weeks following service of the notice, the offeror must send a copy of it to the company together with the consideration for the ordinary shares to which the notice relates, and an instrument of transfer executed on behalf of the outstanding shareholder(s) by a person appointed by the offeror.
- (iii) The company will hold the consideration on trust for the outstanding shareholders.

Sell-out

- (i) Sections 983 to 985 of the Companies Act 2006 also give minority shareholders in the company a right to be bought out in certain circumstances by an offeror who has made a takeover offer. If a takeover offer relating to all the ordinary shares of the company is made at any time before the end of the period within which the offer could be accepted and the offeror held or had agreed to acquire not less than 90% of the ordinary shares, any holder of shares to which the offer related who had not accepted the offer could by a written communication to the offeror require it to acquire those shares. The offeror is required to give any shareholder notice of his right to be bought out within one month of that right arising. The offeror may impose a time limit on the rights of minority shareholders to be bought out, but that period cannot end less than three months after the end of the acceptance period, or, if longer a period of three months from the date of the notice.
- (ii) If a shareholder exercises his rights, the offeror is bound to acquire those shares on the terms of the offer or on such other terms as may be agreed.

Differences in corporate law

The applicable provisions of the Companies Act 2006 differ from laws applicable to U.S. corporations and their shareholders. Set forth below is a summary of certain differences between the provisions of the Companies Act 2006 applicable to us and the General Corporation Law of the State of Delaware relating to shareholders' rights and protections. This summary is not intended to be a complete discussion of the respective rights and it is qualified in its entirety by reference to Delaware law and English law.

	England and Wales	Delaware
Number of Directors	Under the Companies Act 2006, a public limited company must have at least two directors and the number of directors may be fixed by or in the manner provided in a company's articles of association.	Under Delaware law, a corporation must have at least one director and the number of directors shall be fixed by or in the manner provided in the bylaws.
Removal of Directors	Under the Companies Act 2006, shareholders may remove a director without cause by an ordinary resolution (which is passed by a simple majority of those voting in person or by proxy at a general meeting) irrespective of any provisions of any service contract the director has with the company, provided 28 clear days' notice of the resolution has been given to the company and its shareholders. On receipt of notice of an intended resolution to remove a director, the company must forthwith send a copy of the notice to the director concerned. Certain other procedural requirements	Under Delaware law, any director or the entire board of directors may be removed, with or without cause, by the holders of a majority of the shares then entitled to vote at an election of directors, except (i) unless the certificate of incorporation provides otherwise, in the case of a corporation whose board of directors is classified, stockholders may effect such removal only for cause, or (ii) in the case of a corporation having cumulative voting, if less than the entire board of directors is to be removed, no director may be

	England and Wales	Delaware
	<p>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.</p>	<p>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.</p>
Vacancies on the Board of Directors	<p>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.</p>	<p>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.</p>
Annual General Meeting	<p>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.</p>	<p>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.</p>
General Meeting	<p>Under the Companies Act 2006, a general meeting of the shareholders of a public limited company may be called by the directors.</p> <p>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</p>	<p>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.</p>

	England and Wales	Delaware
Notice of General Meetings	<p>certain period, may themselves convene a general meeting.</p> <p>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.</p>	<p>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.</p>
Proxy	<p>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.</p>	<p>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.</p>
Preemptive Rights	<p>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</p>	<p>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.</p>

	England and Wales	Delaware
	securities into, ordinary shares, proposed to be allotted for cash must be offered first to the existing equity shareholders in the company in proportion to the respective nominal value of their holdings, unless an exception applies or a special resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise in each case in accordance with the provisions of the Companies Act.	
Authority to Allot	Under the Companies Act 2006, the directors of a company must not allot shares or grant rights to subscribe for or convert any security into shares unless an exception applies or an ordinary resolution to the contrary has been passed by shareholders in a general meeting or the articles of association provide otherwise, in each case in accordance with the provisions of the Companies Act.	Under Delaware law, if the corporation's charter or certificate of incorporation so provides, the board of directors has the power to authorize the issuance of stock. The board may authorize capital stock to be issued for consideration consisting of cash, any tangible or intangible property or any benefit to the corporation or any combination thereof. It may determine the amount of such consideration by approving a formula. In the absence of actual fraud in the transaction, the judgment of the directors as to the value of such consideration is conclusive.
Liability of Directors and Officers	Under the Companies Act 2006, any provision, whether contained in a company's articles of association or any contract or otherwise, that purports to exempt a director of a company, to any extent, from any liability that would otherwise attach to him in connection with any negligence, default, breach of duty or breach of trust in relation to the company, is void. Any provision by which a company directly or indirectly provides an indemnity, to any extent, for a director of the company or of an associated company against any liability attaching to him in connection with any	Under Delaware law, a corporation's certificate of incorporation may include a provision eliminating or limiting the personal liability of a director to the corporation and its stockholders for damages arising from a breach of fiduciary duty as a director. However, no provision can limit the liability of a director for: <ul style="list-style-type: none">• any breach of the director's duty of loyalty to the corporation or its stockholders;• acts or omissions not in good faith or that involve intentional

	England and Wales	Delaware
	<p>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.</p>	<p>misconduct or a knowing violation of law;</p> <ul style="list-style-type: none">• intentional or negligent payment of unlawful dividends or stock purchases or redemptions; or• any transaction from which the director derives an improper personal benefit.
Voting Rights	<p>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</p>	<p>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.</p>

	England and Wales	Delaware
	<p>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.</p> <p>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.</p>	
Shareholder Vote on Certain Transactions	<p>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:</p> <ul style="list-style-type: none">• 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.	<p>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:</p> <ul style="list-style-type: none">• 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	<p>Under English law, a director owes various statutory and fiduciary duties to the company, including:</p> <ul style="list-style-type: none">• 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.	<p>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.</p> <p>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</p> <p>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.</p>

	England and Wales	Delaware
Stockholder Suits	<p>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.</p>	<p>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.</p> <p>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:</p> <ul style="list-style-type: none">• state that the plaintiff was a stockholder at the time of the transaction of which the plaintiff complains or that the plaintiff's 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. <p>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.</p>

Stock exchange listing

We have been approved to list our ADSs on the Nasdaq Global Select Market under the symbol "ORTX."

Transfer agent and registrar of shares

Our share register will be maintained by Equiniti Limited upon the closing of this offering. The share register reflects only record owners of our ordinary shares. Holders of our ADSs will not be treated as our shareholders and their names will therefore not be entered in our share register. The depositary, the custodian or their nominees will be the holder of the ordinary shares underlying our ADSs. Holders of our ADSs have a right to receive the ordinary shares underlying their ADSs. For discussion on our ADSs and ADS holder rights, see "Description of American depositary shares" in this prospectus.

Description of American depositary shares

American depositary shares

Citibank, N.A., or Citibank, has agreed to act as the depositary for the ADSs. Citibank's depositary offices are located at, 388 Greenwich Street, New York, New York 10013. ADSs represent ownership interests in securities that are on deposit with the depositary. ADSs may be represented by certificates that are commonly known as American Depositary Receipts, or ADRs. The depositary typically appoints a custodian to safekeep the securities on deposit. In this case, the custodian is Citibank, N.A., London Branch, located at 25 Canada Square, Canary Wharf, London, E14 5LB, United Kingdom.

We have appointed Citibank as depositary pursuant to a deposit agreement. A copy of the deposit agreement is on file with the SEC under cover of a registration statement on Form F-6. You may obtain a copy of the deposit agreement from the SEC's Public Reference Room at 100 F Street, N.E., Washington, D.C. 20549 and from the SEC's website (www.sec.gov). Please refer to registration number 333-227905 when retrieving such copy.

We are providing you with a summary description of the material terms of the ADSs and of your material rights as an owner of ADSs. Please remember that summaries by their nature lack the precision of the information summarized and that the rights and obligations of an owner of ADSs will be determined by reference to the terms of the deposit agreement and not by this summary. We urge you to review the deposit agreement in its entirety.

Each ADS represents the right to receive, and to exercise the beneficial ownership interests in, one ordinary share that is on deposit with the depositary and/or custodian. An ADS also represents the right to receive, and to exercise the beneficial interests in, any other property received by the depositary or the custodian on behalf of the owner of the ADS but that has not been distributed to the owners of ADSs because of legal restrictions or practical considerations. We and the depositary may agree to change the ADS-to-ordinary share ratio by amending the deposit agreement. This amendment may give rise to, or change, the depositary fees payable by ADS owners. The custodian, the depositary and their respective nominees will hold all deposited property for the benefit of the holders and beneficial owners of ADSs. The deposited property does not constitute the proprietary assets of the depositary, the custodian or their nominees. Beneficial ownership in the deposited property will under the terms of the deposit agreement be vested in the beneficial owners of the ADSs. The depositary, the custodian and their respective nominees will be the record holders of the deposited property represented by the ADSs for the benefit of the holders and beneficial owners of the corresponding ADSs. A beneficial owner of ADSs may or may not be the holder of ADSs. Beneficial owners of ADSs will be able to receive, and to exercise beneficial ownership interests in, the deposited property only through the registered holders of the ADSs, the registered holders of the ADSs (on behalf of the applicable ADS owners) only through the depositary, and the depositary (on behalf of the owners of the corresponding ADSs) directly, or indirectly, through the custodian or their respective nominees, in each case upon the terms of the deposit agreement.

If you become an owner of ADSs, you will become a party to the deposit agreement and therefore will be bound to its terms and to the terms of any ADR that represents your ADSs. The deposit agreement and the ADR specify our rights and obligations as well as your rights and obligations as owner of ADSs and those of the depositary. As an ADS holder you appoint the depositary to act on your behalf in certain circumstances. The deposit agreement and the ADRs

[Table of Contents](#)

are governed by New York law. However, our obligations to the holders of ordinary shares will continue to be governed by the laws of England and Wales, which may be different from the laws of the United States.

In addition, applicable laws and regulations may require you to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. You are solely responsible for complying with such reporting requirements and obtaining such approvals. Neither the depositary, the custodian, us or any of their or our respective agents or affiliates shall be required to take any actions whatsoever on your behalf to satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

As an owner of ADSs, we will not treat you as one of our shareholders and you will not have direct shareholder rights. The depositary will hold on your behalf the shareholder rights attached to the ordinary shares underlying your ADSs. As an owner of ADSs you will be able to exercise the shareholders rights for the ordinary shares represented by your ADSs through the depositary only to the extent contemplated in the deposit agreement. To exercise any shareholder rights not contemplated in the deposit agreement you will, as an ADS owner, need to arrange for the cancellation of your ADSs and become a direct shareholder.

The manner in which you own the ADSs (e.g., in a brokerage account vs. as registered holder, or as holder of certificated vs. uncertificated ADSs) may affect your rights and obligations, and the manner in which, and extent to which, the depositary's services are made available to you. As an owner of ADSs, you may hold your ADSs either by means of an ADR registered in your name, through a brokerage or safekeeping account, or through an account established by the depositary in your name reflecting the registration of uncertificated ADSs directly on the books of the depositary (commonly referred to as the direct registration system or DRS). The direct registration system reflects the uncertificated (book-entry) registration of ownership of ADSs by the depositary. Under the direct registration system, ownership of ADSs is evidenced by periodic statements issued by the depositary to the holders of the ADSs. The direct registration system includes automated transfers between the depositary and The Depository Trust Company, or DTC, the central book-entry clearing and settlement system for equity securities in the United States. If you decide to hold your ADSs through your brokerage or safekeeping account, you must rely on the procedures of your broker or bank to assert your rights as ADS owner. Banks and brokers typically hold securities such as the ADSs through clearing and settlement systems such as DTC. The procedures of such clearing and settlement systems may limit your ability to exercise your rights as an owner of ADSs. Please consult with your broker or bank if you have any questions concerning these limitations and procedures. All ADSs held through DTC will be registered in the name of a nominee of DTC. This summary description assumes you have opted to own the ADSs directly by means of an ADS registered in your name and, as such, we will refer to you as the "holder." When we refer to "you," we assume the reader owns ADSs and will own ADSs at the relevant time.

The registration of the ordinary shares in the name of the depositary or the custodian shall, to the maximum extent permitted by applicable law, vest in the depositary or the custodian the record ownership in the applicable ordinary shares with the beneficial ownership rights and interests in such ordinary shares being at all times vested with the beneficial owners of the ADSs representing the ordinary shares. The depositary or the custodian shall at all times be entitled to exercise the beneficial ownership rights in all deposited property, in each case only on behalf of the holders and beneficial owners of the ADSs representing the deposited property.

Dividends and other distributions

As a holder of ADSs, you generally have the right to receive the distributions we make on the securities deposited with the custodian. Your receipt of these distributions may be limited, however, by practical considerations and legal limitations. Holders of ADSs will receive such distributions under the terms of the deposit agreement in proportion to the number of ADSs held as of the specified record date, after deduction the applicable fees, taxes and expenses.

Distributions of cash

Whenever we make a cash distribution for the securities on deposit with the custodian, we will deposit the funds with the custodian. Upon receipt of confirmation of the deposit of the requisite funds, the depository will arrange for the funds received in a currency other than U.S. dollars to be converted into U.S. dollars and for the distribution of the U.S. dollars to the holders, subject to the laws and regulations of England and Wales.

The conversion into U.S. dollars will take place only if practicable and if the U.S. dollars are transferable to the United States. The depository 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 depository 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 depository 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 depository 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 depository 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 depository does not distribute new ADSs as described above, it may sell the ordinary shares received upon the terms described in the deposit agreement and will distribute the proceeds of the sale as in the case of a distribution of cash.

Distributions of rights

Whenever we intend to distribute rights to purchase additional ordinary shares, we will give prior notice to the depositary and we will assist the depositary in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depositary will establish procedures to distribute rights to purchase additional ADSs to holders and to enable such holders to exercise such rights if it is lawful and reasonably practicable to make the rights available to holders of ADSs, and if we provide all of the documentation contemplated in the deposit agreement (such as opinions to address the lawfulness of the transaction). You may have to pay fees, expenses, taxes and other governmental charges to subscribe for the new ADSs upon the exercise of your rights. The depositary is not obligated to establish procedures to facilitate the distribution and exercise by holders of rights to purchase new ordinary shares other than in the form of ADSs.

The depositary will *not* distribute the rights to you if:

- we do not timely request that the rights be distributed to you or we request that the rights not be distributed to you;
- we fail to deliver satisfactory documents to the depositary; or
- it is not reasonably practicable to distribute the rights.

The depositary will sell the rights that are not exercised or not distributed if such sale is lawful and reasonably practicable. The proceeds of such sale will be distributed to holders as in the case of a cash distribution. If the depositary is unable to sell the rights, it will allow the rights to lapse.

Elective Distributions

Whenever we intend to distribute a dividend payable at the election of shareholders either in cash or in additional shares, we will give prior notice thereof to the depositary and will indicate whether we wish the elective distribution to be made available to you. In such case, we will assist the depositary in determining whether such distribution is lawful and reasonably practicable.

The depositary will make the election available to you only if it is reasonably practicable and if we have provided all of the documentation contemplated in the deposit agreement. In such case, the depositary will establish procedures to enable you to elect to receive either cash or additional ADSs, in each case as described in the deposit agreement.

If the election is not made available to you, you will receive either cash or additional ADSs, depending on what a shareholder in England and Wales would receive upon failing to make an election, as more fully described in the deposit agreement.

Other Distributions

Whenever we intend to distribute property other than cash, ordinary shares or rights to purchase additional ordinary shares, we will notify the depositary in advance and will indicate whether we wish such distribution to be made to you. If so, we will assist the depositary in determining whether such distribution to holders is lawful and reasonably practicable.

If it is reasonably practicable to distribute such property to you and if we provide all of the documentation contemplated in the deposit agreement, the depositary will distribute the property to the holders in a manner it deems practicable.

[Table of Contents](#)

The distribution will be made net of fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes and governmental charges, the depositary may sell all or a portion of the property received.

The depositary will *not* distribute the property to you and will sell the property if:

- we do not request that the property be distributed to you or if we ask that the property not be distributed to you; or
- we do not deliver satisfactory documents to the depositary; or
- the depositary determines that all or a portion of the distribution to you is not reasonably practicable.

The proceeds of such a sale will be distributed to holders as in the case of a cash distribution.

Redemption

Whenever we decide to redeem any of the ordinary shares on deposit with the custodian, we will notify the depositary in advance. If it is practicable and if we provide all of the documentation contemplated in the deposit agreement, the depositary will provide notice of the redemption to the holders.

The custodian will be instructed to surrender the ordinary shares being redeemed against payment of the applicable redemption price. The depositary will convert the redemption funds received into U.S. dollars upon the terms of the deposit agreement and will establish procedures to enable holders to receive the net proceeds from the redemption upon surrender of their ADSs to the depositary. You may have to pay fees, expenses, taxes and other governmental charges upon the redemption of your ADSs. If less than all ADSs are being redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as the depositary may determine.

Changes affecting ordinary shares

The ordinary shares held on deposit for your ADSs may change from time to time. For example, there may be a change in nominal or par value, split-up, cancellation, consolidation, or any other reclassification of such ordinary shares or a recapitalization, reorganization, merger, consolidation, or sale of assets of our company.

If any such change were to occur, your ADSs would, to the extent permitted by law, represent the right to receive the property received or exchanged in respect of the ordinary shares held on deposit. The depositary may in such circumstances deliver new ADSs to you, amend the deposit agreement, the ADRs and the applicable Registration Statement(s) on Form F-6, call for the exchange of your existing ADSs for new ADSs and take any other actions that are appropriate to reflect as to the ADSs the change affecting the ordinary shares. If the depositary may not lawfully distribute such property to you, the depositary may sell such property and distribute the net proceeds to you as in the case of a cash distribution.

Issuance of ADSs upon deposit of ordinary shares

Upon completion of this offering, the ordinary shares being offered pursuant to this prospectus will be deposited by us with the custodian. Upon receipt of confirmation of such deposit, the depositary will issue ADSs to the underwriters named in this prospectus.

After the closing of this offering, the depositary may create ADSs on your behalf if you or your broker deposit ordinary shares with the custodian. The depositary will deliver these ADSs to the person you indicate only after you pay any applicable issuance fees and any charges and taxes payable for the transfer of the ordinary shares to the custodian. Your ability to deposit ordinary shares and receive ADSs may be limited by the legal considerations in the United States and England and Wales applicable at the time of deposit.

The issuance of ADSs may be delayed until the depositary or the custodian receives confirmation that all required approvals have been given and that the ordinary shares have been duly transferred to the custodian. The depositary will only issue ADSs in whole numbers.

When you make a deposit of ordinary shares, you will be responsible for transferring good and valid title to the depositary. As such, you will be deemed to represent and warrant that:

- the ordinary shares are duly authorized, validly issued, fully paid, non-assessable, and legally obtained;
- all preemptive (and similar) rights, if any, with respect to such ordinary shares have been validly waived or exercised;
- you are duly authorized to deposit the ordinary shares;
- the ordinary shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage, or adverse claim, and are not, and the ADSs issuable upon such deposit will not be, "restricted securities" (as defined in the deposit agreement);
- the ordinary shares presented for deposit have not been stripped of any rights or entitlements; and
- the deposit of shares does not violate any applicable provision of English law.

If any of the representations or warranties are incorrect in any way, we and the depositary may, at your cost and expense, take any and all actions necessary to correct the consequences of the misrepresentations.

Transfer, combination and split up of ADRs

As an ADR holder, you will be entitled to transfer, combine or split up your ADRs and the ADSs evidenced thereby. For transfers of ADRs, you will have to surrender the ADRs to be transferred to the depositary and also must:

- ensure that the surrendered ADR is properly endorsed or otherwise in proper form for transfer;
- provide such proof of identity and genuineness of signatures as the depositary deems appropriate;
- provide any transfer stamps required by the State of New York or the United States; and
- pay all applicable fees, charges, expenses, taxes, and other government charges payable by ADR holders pursuant to the terms of the deposit agreement, upon the transfer of ADRs.

To have your ADRs either combined or split up, you must surrender the ADRs in question to the depositary with your request to have them combined or split up, and you must pay all applicable fees, charges and expenses payable by ADR holders, pursuant to the terms of the deposit agreement, upon a combination or split up of ADRs.

Withdrawal of ordinary shares upon cancellation of ADSs

As a holder, you will be entitled to present your ADSs to the depository for cancellation and then receive the corresponding number of underlying ordinary shares at the custodian's offices. Your ability to withdraw the ordinary shares held in respect of the ADSs may be limited by the legal consideration in the United States and England and Wales applicable at the time of withdrawal. In order to withdraw the ordinary shares represented by your ADSs, you will be required to pay to the depository 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 depository may ask you to provide proof of identity and genuineness of any signature and such other documents as the depository may deem appropriate before it will cancel your ADSs. The withdrawal of the ordinary shares represented by your ADSs may be delayed until the depository receives satisfactory evidence of compliance with all applicable laws and regulations. Please keep in mind that the depository will only accept ADSs for cancellation that represent a whole number of securities on deposit.

You will have the right to withdraw the securities represented by your ADSs at any time except as a result of:

- temporary delays that may arise because (i) the transfer books for the ordinary shares or ADSs are closed, or (ii) ordinary shares are immobilized on account of a shareholders' meeting or a payment of dividends;
- obligations to pay fees, taxes and similar charges;
- restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit; and
- other circumstances specifically contemplated by Section I.A.(I) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time)

The deposit agreement may not be modified to impair your right to withdraw the ordinary shares represented by your ADSs except to comply with mandatory provisions of law.

Voting rights

As a holder, you generally have the right under the deposit agreement to instruct the depository 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 depository will distribute to you any notice of shareholders' meeting received from us together with information explaining how to instruct the depository to exercise the voting rights of the ordinary shares represented by ADSs. In lieu of distributing such materials, the depository bank may distribute to holders of ADSs instructions on how to retrieve such materials upon request.

[Table of Contents](#)

If the depositary timely receives voting instructions from a holder of ADSs, it will endeavor to vote (or cause the custodian to vote) the securities (in person or by proxy) represented by the holder's ADSs as follows:

- *In the event of voting by show of hands*, the depositary will vote (or cause the custodian to vote) all ordinary shares represented by ADSs in accordance with the voting instructions received from a majority of holders of ADSs who provide timely voting instructions.
- In the event of voting by poll, the depositary will vote (or cause the custodian to vote) the ordinary shares represented by ADSs in accordance with the voting instructions received from the holders of ADSs.

Securities for which no voting instructions have been received will not be voted (except as otherwise contemplated in the deposit agreement). Please note that the ability of the depositary to carry out voting instructions may be limited by practical and legal limitations and the terms of the securities on deposit. We cannot assure you that you will receive voting materials in time to enable you to return voting instructions to the depositary in a timely manner.

Fees and charges

As an ADS holder, you will be required to pay the following fees under the terms of the deposit agreement:

Service	Fee
Issuance of ADSs (e.g., an issuance of ADS upon a deposit of ordinary shares or upon a change in the ADS(s)-to-ordinary shares ratio), excluding ADS issuances as a result of distributions of ordinary shares	Up to \$0.05 per ADS issued
Cancellation of ADSs (e.g., a cancellation of ADSs for delivery of deposited property or upon a change in the ADS(s)-to-ordinary shares ratio)	Up to \$0.05 per ADS cancelled
Distribution of cash dividends or other cash distributions (e.g., upon a sale of rights and other entitlements)	Up to \$0.05 per ADS held
Distribution of ADSs pursuant to (i) share dividends or other free share distributions, or (ii) exercise of rights to purchase additional ADSs	Up to \$0.05 per ADS held
Distribution of securities other than ADSs or rights to purchase additional ADSs (e.g., upon a spin-off)	Up to \$0.05 per ADS held
ADS Services	Up to \$0.05 per ADS held on the applicable record date(s) established by the depositary

As an ADS holder you will also be responsible to pay certain charges such as:

- taxes (including applicable interest and penalties) and other governmental charges;

[Table of Contents](#)

- the registration fees as may from time to time be in effect for the registration of ordinary shares on the share register and applicable to transfers of ordinary shares to or from the name of the custodian, the depositary, or any nominees upon the making of deposits and withdrawals, respectively;
- certain cable, telex and facsimile transmission and delivery expenses;
- the expenses and charges incurred by the depositary in the conversion of foreign currency;
- the fees and expenses incurred by the depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to ordinary shares, ADSs and ADRs; and
- the fees and expenses incurred by the depositary, the custodian or any nominee in connection with the servicing or delivery of deposited property.

ADS fees and charges payable upon (i) the issuance of ADSs, and (ii) the cancellation of ADSs are charged to the person for whom the ADSs are issued (in the case of ADS issuances) and to the person for whom ADSs are cancelled (in the case of ADS cancellations). In the case of ADSs issued by the depositary into DTC, the ADS issuance and cancellation fees and charges may be deducted from distributions made through DTC, and may be charged to the DTC participant(s) receiving the ADSs being issued or the DTC participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the beneficial owner(s) and will be charged by the DTC participant(s) to the account of the applicable beneficial owner(s) in accordance with the procedures and practices of the DTC participants as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are charged to the holders as of the applicable ADS record date. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, holders as of the ADS record date will be invoiced for the amount of the ADS fees and charges and such ADS fees and charges may be deducted from distributions made to holders of ADSs. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC participants in accordance with the procedures and practices prescribed by DTC and the DTC participants in turn charge the amount of such ADS fees and charges to the beneficial owners for whom they hold ADSs.

In the event of refusal to pay the depositary fees, the depositary may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary fees from any distribution to be made to the ADS holder. Certain depositary fees and charges (such as the ADS services fee) may become payable shortly after the closing of the ADS offering. Note that the fees and charges you may be required to pay may vary over time and may be changed by us and by the depositary. You will receive prior notice of such changes. The depositary may reimburse us for certain expenses incurred by us in respect of the ADR program, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as we and the depositary agree from time to time.

Amendments and termination

We may agree with the depositary to modify the deposit agreement at any time without your consent. We undertake to give holders 30 days' prior notice of any modifications that would

[Table of Contents](#)

materially prejudice any of their substantial rights under the deposit agreement. We will not consider to be materially prejudicial to your substantial rights any modifications or supplements that are reasonably necessary for the ADSs to be registered under the Securities Act or to be eligible for book-entry settlement, in each case without imposing or increasing the fees and charges you are required to pay. In addition, we may not be able to provide you with prior notice of any modifications or supplements that are required to accommodate compliance with applicable provisions of law.

You will be bound by the modifications to the deposit agreement if you continue to hold your ADSs after the modifications to the deposit agreement become effective. The deposit agreement cannot be amended to prevent you from withdrawing the ordinary shares represented by your ADSs (except as permitted by law).

We have the right to direct the depositary to terminate the deposit agreement. Similarly, the depositary may in certain circumstances on its own initiative terminate the deposit agreement. In either case, the depositary must give notice to the holders at least 30 days before termination. Until termination, your rights under the deposit agreement will be unaffected.

Termination

After termination, the depositary will continue to collect distributions received (but will not distribute any such property until you request the cancellation of your ADSs) and may sell the securities held on deposit. After the sale, the depositary will hold the proceeds from such sale and any other funds then held for the holders of ADSs in a non-interest bearing account. At that point, the depositary will have no further obligations to holders other than to account for the funds then held for the holders of ADSs still outstanding (after deduction of applicable fees, taxes and expenses).

In connection with the termination of the deposit agreement, the depositary may, independently and without the need for any action by us, make available to holders a means to withdraw the ordinary shares and other deposited securities represented by their ADSs and to direct the deposit of such ordinary shares and other deposited securities into an unsponsored ADS program established by the depositary, upon such terms and conditions as the depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored ADS program under the Securities Act, and to receipt by the depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the depositary.

Books of depositary

The depositary will maintain ADS holder records at its depositary office. You may inspect such records at such office during regular business hours but solely for the purpose of communicating with other holders in the interest of business matters relating to the ADSs and the deposit agreement.

The depositary will maintain in New York facilities to record and process the issuance, cancellation, combination, split-up and transfer of ADSs. These facilities may be closed from time to time, to the extent not prohibited by law.

Transmission of notices, reports and proxy soliciting material

The depositary will make available for your inspection at its office all communications that it receives from us as a holder of deposited securities that we make generally available to holders of deposited securities. Subject to the terms of the deposit agreement, the depositary will send you copies of those communications or otherwise make those communications available to you if we ask it to.

Limitations on obligations and liabilities

The deposit agreement limits our obligations and the depositary's obligations to you. Please note the following:

- We and the depositary are obligated only to take the actions specifically stated in the deposit agreement without negligence or bad faith.
- The depositary disclaims any liability for any failure to carry out voting instructions, for any manner in which a vote is cast or for the effect of any vote, provided it acts in good faith and in accordance with the terms of the deposit agreement.
- The depositary disclaims any liability for any failure to determine the lawfulness or practicality of any action, for the content of any document forwarded to you on our behalf or for the accuracy of any translation of such a document, for the investment risks associated with investing in ordinary shares, for the validity or worth of the ordinary shares, for any tax consequences that result from the ownership of ADSs, for the credit-worthiness of any third party, for allowing any rights to lapse under the terms of the deposit agreement, for the timeliness of any of our notices or for our failure to give notice.
- We and the depositary will not be obligated to perform any act that is inconsistent with the terms of the deposit agreement.
- We and the depositary disclaim any liability if we or the depositary are prevented or forbidden from or subject to any civil or criminal penalty or restraint on account of, or delayed in, doing or performing any act or thing required by the terms of the deposit agreement, by reason of any provision, present or future of any law or regulation, or by reason of present or future provision of any provision of our Articles of Association or any provision of or governing the securities on deposit, or by reason of any act of God or war or other circumstances beyond our control.
- We and the depositary disclaim any liability by reason of any exercise of, or failure to exercise, any discretion provided for in the deposit agreement or in our Articles of Association or in any provisions of or governing the securities on deposit.
- We and the depositary further disclaim any liability for any action or inaction in reliance on the advice or information received from legal counsel, accountants, any person presenting ordinary shares for deposit, any holder of ADSs or authorized representatives thereof, or any other person believed by either of us in good faith to be competent to give such advice or information.
- We and the depositary also disclaim liability for the inability by a holder to benefit from any distribution, offering, right or other benefit that is made available to holders of ordinary shares but is not, under the terms of the deposit agreement, made available to you.

[Table of Contents](#)

- We and the depositary may rely without any liability upon any written notice, request or other document believed to be genuine and to have been signed or presented by the proper parties.
- We and the depositary also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.
- No disclaimer of any Securities Act liability is intended by any provision of the deposit agreement.

Nothing in the deposit agreement gives rise to a partnership or joint venture, or establishes a fiduciary relationship, among us, the depositary bank and you as ADS holder.

Nothing in the deposit agreement precludes Citibank (or its affiliates) from engaging in transactions in which parties adverse to us or the ADS owners have interests, and nothing in the deposit agreement obligates Citibank to disclose those transactions, or any information obtained in the course of those transactions, to us or to the ADS owners, or to account for any payment received as part of those transactions.

Taxes

You will be responsible for the taxes and other governmental charges payable on the ADSs and the ordinary shares represented by the ADSs. We, the depositary and the custodian may deduct from any distribution the taxes and governmental charges payable by holders and may sell any and all property on deposit to pay the taxes and governmental charges payable by holders. You will be liable for any deficiency if the sale proceeds do not cover the taxes that are due.

The depositary may refuse to issue ADSs, to deliver, transfer, split and combine ADRs or to release securities on deposit until all taxes and charges are paid by the applicable holder. The depositary and the custodian may take reasonable administrative actions to obtain tax refunds and reduced tax withholding for any distributions on your behalf. However, you may be required to provide to the depositary and to the custodian proof of taxpayer status and residence and such other information as the depositary and the custodian may require to fulfill legal obligations. You are required to indemnify us, the depositary and the custodian for any claims with respect to taxes based on any tax benefit obtained for you.

Foreign currency conversion

The depositary will arrange for the conversion of all foreign currency received into U.S. dollars if such conversion is practical, and it will distribute the U.S. dollars in accordance with the terms of the deposit agreement. You may have to pay fees and expenses incurred in converting foreign currency, such as fees and expenses incurred in complying with currency exchange controls and other governmental requirements.

If the conversion of foreign currency is not practical or lawful, or if any required approvals are denied or not obtainable at a reasonable cost or within a reasonable period, the depositary may take the following actions in its discretion:

- Convert the foreign currency to the extent practical and lawful and distribute the U.S. dollars to the holders for whom the conversion and distribution is lawful and practical.
- Distribute the foreign currency to holders for whom the distribution is lawful and practical.
- Hold the foreign currency (without liability for interest) for the applicable holders.

Governing Law/Waiver of Jury Trial

The deposit agreement, the ADRs and ADSs will be interpreted in accordance with the laws of the State of New York. The rights of holders of ordinary shares (including ordinary shares represented by ADSs) are governed by the laws of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, YOU IRREVOCABLY WAIVE YOUR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT, THE ADRs AND ADSs AGAINST US AND/OR THE DEPOSITARY. If we or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable in the facts and circumstances of that case in accordance with applicable case law. However, you will not be deemed by agreeing to the terms of the deposit agreement to have waived our or the depositary's compliance with U.S. federal securities laws and the rules and regulations promulgated thereunder.

Shares and ADSs eligible for future sale

Prior to this offering, there has been no public market for our ordinary shares or ADSs. Upon completion of this offering, and assuming no exercise of the underwriters' option to purchase additional ADSs, we will have 84,047,200 ADSs outstanding, representing 84,047,200 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 14,285,715 ADSs, or 16,428,572 ADSs if the underwriters exercise in full their option to purchase additional ADSs, sold in this offering will be freely transferable without restriction, except for any shares purchased by one or more of our existing "affiliates," as that term is defined in Rule 144 under the Securities Act. We expect approximately 69,761,485 ADSs will be subject to the contractual 180-day lock-up period described below. This may adversely affect the prevailing market price of our ADSs and our ability to raise equity capital in the future.

Rule 144

In general, persons who have beneficially owned restricted ordinary shares for at least six months, and any affiliate of the company who owns either restricted or unrestricted securities, are entitled to sell their securities without registration with the SEC under an exemption from registration provided by Rule 144 under the Securities Act.

Non-Affiliates

Any person who is not deemed to have been one of our affiliates at the time of, or at any time during the three months preceding, a sale may sell an unlimited number of restricted securities under Rule 144 if:

- the restricted securities have been held for at least six months, including the holding period of any prior owner other than one of our affiliates;
- we have been subject to the Exchange Act periodic reporting requirements for at least 90 days before the sale; and
- we are current in our Exchange Act reporting at the time of sale.

Any person who is not deemed to have been an affiliate of ours at the time of, or at any time during the three months preceding, a sale and has held the restricted securities for at least one year, including the holding period of any prior owner other than one of our affiliates, will be entitled to sell an unlimited number of restricted securities without regard to the length of time we have been subject to Exchange Act periodic reporting or whether we are current in our Exchange Act reporting.

Affiliates

Persons seeking to sell restricted securities who are our affiliates at the time of, or any time during the three months preceding, a sale, would be subject to the restrictions described above.

[Table of Contents](#)

They are also subject to additional restrictions, by which such person would be required to comply with the manner of sale and notice provisions of Rule 144 and would be entitled to sell within any three-month period only that number of securities that does not exceed the greater of either of the following:

- 1% of the number of ordinary shares then outstanding, which will equal approximately 830,948 shares immediately after the closing of this offering based on the number of ordinary shares outstanding as of September 30, 2018; or
- the average weekly trading volume of our ordinary shares in the form of ADSs on the Nasdaq Global Select 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.

[Table of Contents](#)

The discussion is based on the Code, administrative pronouncements, judicial decisions, final, temporary and proposed Treasury Regulations, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as of the date hereof, changes to any of which may affect the tax consequences described herein—possibly with retroactive effect.

A “U.S. Holder” is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

- (i) An individual who is a citizen or individual resident of the United States;
- (ii) a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;
- (iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or
- (iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

We do not believe that we were a PFIC in the 2017 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a "controlled foreign corporation" for any taxable year (see discussion below in "Controlled foreign corporation considerations"), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a "deemed sale" election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the "deemed sale" election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder's ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any "excess distribution" the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any "excess distribution" such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute "marketable" securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder's holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder's holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and

[Table of Contents](#)

- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or “excess distribution” cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF Election. In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are “marketable.” Ordinary shares or ADSs will be marketable if they are “regularly traded” on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, and you are a holder of ADSs, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder’s adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder’s adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves “marketable.” As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax

advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an annual report containing such information as the U.S. Treasury may require. A U.S. Holder's failure to file the annual report will cause the statute of limitations for such U.S. Holder's U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the annual report, and, unless such failure is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder's entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE YOU TO CONSULT YOUR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO YOUR INVESTMENT IN THE ORDINARY SHARES OR ADSs.

Controlled foreign corporation considerations

Each "Ten Percent Shareholder" (as defined below) in a non-U.S. corporation that is classified as a "controlled foreign corporation," or a CFC, for U.S. federal income tax purposes generally is required to include in income each year for U.S. federal tax purposes such Ten Percent Shareholder's pro rata share of certain types of income earned by the CFC, including "Subpart F income," "global intangible low-taxed income" and certain other income generated by the CFC, even if the CFC has made no distributions to its shareholders. In addition, a Ten Percent Shareholder that realizes gain from the sale or exchange of shares in the CFC may be required to classify a portion of such gain as dividend income rather than capital gain (see discussion below in "Taxation of distributions" regarding the tax treatment of dividend income). A non-U.S. corporation generally will be classified as a CFC for U.S. federal income tax purposes if Ten Percent Shareholders own, directly or indirectly, more than 50% of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation. A "Ten Percent Shareholder" is a United States person (as defined by the Code) who owns or is considered to own 10% or more of either the total combined voting power of all classes of stock of such corporation entitled to vote or of the total value of the stock of such corporation.

We believe that we were not a CFC in the 2017 taxable year, though we have not made a determination regarding our CFC status in the current taxable year, and we may become a CFC in a subsequent taxable year. The determination of CFC status is complex and includes attribution rules, the application of which is not entirely certain. In addition, recent changes to the attribution rules relating to the determination of CFC status may make it difficult to determine our CFC status for any taxable year. It is possible that, following this offering, a shareholder treated as a U.S. person for U.S. federal income tax purposes will acquire, directly or indirectly, enough shares to be treated as a Ten Percent Shareholder. We also believe that immediately following this offering we may have certain shareholders that are Ten Percent Shareholders for U.S. federal income tax purposes. U.S. Holders should consult their own tax advisors with respect to the potential adverse U.S. tax consequences of becoming a Ten Percent Shareholder in a CFC. If we are classified as both a CFC and a PFIC, we generally will not be treated as a PFIC with respect to those U.S. Holders that meet the definition of a Ten Percent Shareholder during the period in which we are a CFC.

Taxation of distributions

Subject to the discussion above under “PFIC rules,” distributions paid on ordinary shares or ADSs, other than certain pro rata distributions of ordinary shares or ADSs, will generally be treated as dividends to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles). Because we may not calculate our earnings and profits under U.S. federal income tax principles, we expect that distributions generally will be reported to U.S. Holders as dividends. Subject to applicable limitations and the discussions above regarding concerns expressed by the U.S. Treasury, dividends paid to certain non-corporate U.S. Holders may be taxable at preferential rates applicable to “qualified dividend income” if we are a “qualified foreign corporation” and certain other requirements are met. However, the qualified dividend income treatment may not apply if we are treated as a PFIC with respect to the U.S. Holder. The amount of the dividend will be treated as foreign-source dividend income to U.S. Holders and will not be eligible for the dividends-received deduction generally available to U.S. corporations under the Code. Dividends will generally be included in a U.S. Holder’s income on the date of the U.S. Holder’s receipt of the dividend. The amount of any dividend income paid in foreign currency will be the U.S. dollar amount calculated by reference to the exchange rate in effect on the date of actual or constructive receipt, regardless of whether the payment is in fact converted into U.S. dollars. If the dividend is converted into U.S. dollars on the date of receipt, a U.S. Holder should not be required to recognize foreign currency gain or loss in respect of the dividend income. A U.S. Holder may have foreign currency gain or loss if the dividend is converted into U.S. dollars after the date of receipt. Such gain or loss would generally be treated as U.S.-source ordinary income or loss. The amount of any distribution of property other than cash (and other than certain pro rata distributions of ordinary shares or ADSs or rights to acquire ordinary shares or ADSs) will be the fair market value of such property on the date of distribution.

For foreign tax credit limitation purposes, our dividends will generally be treated as passive category income. Because no U.K. income taxes will be withheld from dividends on ordinary shares or ADSs, there will be no creditable foreign taxes associated with any dividends that a U.S. Holder will receive. The rules governing foreign tax credits are complex and U.S. Holders should therefore consult their tax advisers regarding the effect of the receipt of dividends for foreign tax credit limitation purposes.

Sale or other taxable disposition of ordinary shares and ADSs

Subject to the discussion above under “PFIC rules,” gain or loss realized on the sale or other taxable disposition of ordinary shares or ADSs will be capital gain or loss, and will be long-term capital gain or loss if the U.S. Holder held the ordinary shares or ADSs for more than one year. The amount of the gain or loss will equal the difference between the U.S. Holder’s tax basis in the ordinary shares or ADSs disposed of and the amount realized on the disposition, in each case as determined in U.S. dollars. This gain or loss will generally be U.S.-source gain or loss for foreign tax credit purposes. The deductibility of capital losses is subject to limitations.

If the consideration received by a U.S. Holder is not paid in U.S. dollars, the amount realized will be the U.S. dollar value of the payment received determined by reference to the spot rate of exchange on the date of the sale or other disposition. However, if the ordinary shares or ADSs are treated as traded on an “established securities market” and you are either a cash basis taxpayer or an accrual basis taxpayer that has made a special election (which must be applied

consistently from year to year and cannot be changed without the consent of the IRS), you will determine the U.S. dollar value of the amount realized in a non-U.S. dollar currency by translating the amount received at the spot rate of exchange on the settlement date of the sale. If you are an accrual basis taxpayer that is not eligible to or does not elect to determine the amount realized using the spot rate on the settlement date, you will recognize foreign currency gain or loss to the extent of any difference between the U.S. dollar amount realized on the date of sale or disposition and the U.S. dollar value of the currency received at the spot rate on the settlement date.

Information reporting and backup withholding

Payments of dividends and sales proceeds that are made within the United States or through certain U.S.-related financial intermediaries generally are subject to information reporting, and may be subject to backup withholding, unless (i) the U.S. Holder is a corporation or other exempt recipient or (ii) in the case of backup withholding, the U.S. Holder provides a correct taxpayer identification number and certifies that it is not subject to backup withholding on a duly executed Form W-9 or otherwise establishes an exemption.

Backup withholding is not an additional tax. The amount of any backup withholding from a payment to a U.S. Holder will be allowed as a credit against the U.S. Holder's U.S. federal income tax liability and may entitle the U.S. Holder to a refund, provided that the required information is timely furnished to the IRS.

Information with respect to foreign financial assets

Certain U.S. Holders who are individuals (and, under regulations, certain entities) may be required to report information relating to the ordinary shares or ADSs, subject to certain exceptions (including an exception for ordinary shares or ADSs held in accounts maintained by certain U.S. financial institutions), by filing IRS Form 8938 (Statement of Specified Foreign Financial Assets) with their federal income tax return. Such U.S. Holders who fail to timely furnish the required information may be subject to a penalty. Additionally, if a U.S. Holder does not file the required information, the statute of limitations with respect to tax returns of the U.S. Holder to which the information relates may not close until three years after such information is filed. U.S. Holders should consult their tax advisers regarding their reporting obligations with respect to their ownership and disposition of the ordinary shares or ADSs.

U.K. Taxation

The following is intended as a general guide to current U.K. tax law and HMRC published practice applying as at the date of this prospectus (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from U.K. taxation. It is written on the basis that the company is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under "Material U.S. federal income tax considerations for U.S. Holders."

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and in the case of individuals, domiciled or

deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment, branch or agency (or equivalent) in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the ADSs or underlying ordinary shares (where the dividends are regarded for U.K. tax purposes as that person's own income). It is assumed that for the purposes of this guide that a holder of an ADS is the beneficial owner of the underlying ordinary share and any dividend income for U.K. direct tax purposes.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- brokers or dealers in securities or persons who hold ADSs otherwise than as an investment;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a permanent establishment, branch or agency to which the ADSs are attributable.

[Table of Contents](#)

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	5,000,000
Goldman Sachs & Co. LLC	4,285,715
Cowen and Company, LLC	3,714,286
Wedbush Securities Inc.	1,285,714
Total	14,285,715

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 \$0.588 per ADS. 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 2,142,857 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.

[Table of Contents](#)

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 \$0.98 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	\$ 0.98	\$ 0.98
Total	\$ 14,000,001	\$ 16,100,001

We estimate that the total expenses of this offering, including registration, filing and listing fees, printing fees and legal and accounting expenses, but excluding the underwriting discounts and commissions, will be approximately \$4.2 million. We have agreed to reimburse the underwriters for expenses incurred by them related to the clearance of this offering with the Financial Industry Regulatory Authority, Inc. in an amount up to \$45,000.

At our request, the underwriters have reserved up to 714,285 ADSs, or 5.0% of the ADSs offered pursuant to this prospectus, for sale at the initial public offering price per ADS through a directed share program, to directors, officers, employees and certain other individuals associated with us. If purchased by these persons, these ADSs will not be subject to a lock-up restriction. The number of ADSs available for sale to the general public will be reduced by the number of reserved ADSs sold to these individuals. Any reserved ADSs not purchased by these individuals will be offered by the underwriters to the general public on the same basis as the other ADSs offered pursuant to this prospectus. The directed share program will be arranged through J.P. Morgan Securities LLC.

A prospectus in electronic format may be made available on the web sites maintained by one or more underwriters, or selling group members, if any, participating in the offering. The underwriters may agree to allocate a number of ADSs to underwriters and selling group members for sale to their online brokerage account holders. Internet distributions will be allocated by the representatives to underwriters and selling group members that may make Internet distributions on the same basis as other allocations.

We have agreed that we will not (i) offer, pledge, announce the intention to sell, sell, contract to sell, sell any option or contract to purchase, purchase any option or contract to sell, grant any option, right or warrant to purchase or otherwise dispose of, directly or indirectly, or file with the SEC a registration statement under the Securities Act relating to, any ADSs or securities convertible into or exchangeable or exercisable for any ADSs, or publicly disclose the intention to make any offer, sale, pledge, disposition or filing, or (ii) enter into any swap or other arrangement that transfers all or a portion of the economic consequences associated with the ownership of any ADSs or any such other securities (regardless of whether any of these transactions are to be settled by the delivery of ADSs or such other securities, in cash or otherwise), in each case without the prior written consent of J.P. Morgan Securities LLC, Goldman Sachs & Co. LLC and Cowen and Company, LLC for a period of 180 days after the date of this prospectus, other than the ADSs to be sold in this offering and any ADSs issued upon the exercise of options granted under our stock plans.

Our directors and executive officers, and certain of our significant shareholders have entered into lock-up agreements with the underwriters prior to the commencement of this offering pursuant

[Table of Contents](#)

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 depository, in exchange for the issuance of ADSs, or the cancellation of ADSs in exchange for the issuance of ordinary shares;
- sales or transfers of ADSs or ordinary shares acquired in this offering or in open market transactions after the consummation of this offering;
- transfers of our ordinary shares or ADSs as a bona fide gift or gifts; by will, other testamentary document or interstate succession to the legal representative, heir, beneficiary or member of the immediate family of the transferor in a transaction not involving a disposition for value; or pursuant to a court order in respect of, or by operation of law as a result of, a divorce, in a transaction not involving a disposition for value;
- transfer of our ordinary shares or ADSs to such person or such person's immediate family members for estate planning purposes;
- transfer of our ordinary shares or ADSs to the members, limited or general partners or shareholders of such person, its direct or indirect affiliates or other entities controlled or managed by the transferor in a transaction not involving a disposition for value;
- in the case of a trust, transfer of our ordinary shares or ADSs to beneficiaries of the transferor in a transaction not involving a disposition for value;
- the receipt of our ordinary shares or ADSs by such person in connection with the conversion of outstanding convertible preferred shares upon the consummation of this offering into ordinary shares;
- the exercise of an option or other equity award to purchase our ordinary shares or ADSs, which are set to expire during the 180-day period following the date of this prospectus;
- any transfer or disposition in connection with any bona fide third-party tender offer, merger, consolidation or other similar transaction that is approved by our board of directors and made to all holders of our ordinary shares or ADSs, the result of which is that a person, or group of persons, other than the Company becomes beneficial owner of more than 50% of our voting stock; and

[Table of Contents](#)

- 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.

Our ADSs have been approved for listing/quotation on Nasdaq under the symbol "ORTX".

In connection with this offering, the underwriters may engage in stabilizing transactions, which involves making bids for, purchasing and selling ADSs in the open market for the purpose of preventing or retarding a decline in the market price of the ADSs while this offering is in progress. These stabilizing transactions may include making short sales of the ADSs, which involves the sale by the underwriters of a greater number of ADSs than they are required to purchase in this offering, and purchasing ADSs on the open market to cover positions created by short sales. Short sales may be "covered" shorts, which are short positions in an amount not greater than the underwriters' option to purchase additional ADSs referred to above, or may be "naked" shorts, which are short positions in excess of that amount. The underwriters may close out any covered short position either by exercising their option to purchase additional ADSs, in whole or in part, or by purchasing ADSs in the open market. In making this determination, the underwriters will consider, among other things, the price of ADSs available for purchase in the open market compared to the price at which the underwriters may purchase ADSs through the option to purchase additional ADSs. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the ADSs in the open market that could adversely affect investors who purchase in this offering. To the extent that the underwriters create a naked short position, they will purchase ADSs in the open market to cover the position.

The underwriters have advised us that, pursuant to Regulation M of the Securities Act, they may also engage in other activities that stabilize, maintain or otherwise affect the price of the ADSs, including the imposition of penalty bids. This means that if the representatives of the underwriters purchase ADSs in the open market in stabilizing transactions or to cover short sales, the representatives can require the underwriters that sold those ADSs as part of this offering to repay the underwriting discount received by them.

These activities may have the effect of raising or maintaining the market price of the ADSs or preventing or retarding a decline in the market price of the ADSs, and, as a result, the price of the ADSs may be higher than the price that otherwise might exist in the open market. If the underwriters commence these activities, they may discontinue them at any time. The underwriters may carry out these transactions on the Nasdaq Global Select 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;

[Table of Contents](#)

- our prospects for future earnings;
- the general condition of the securities markets at the time of this offering;
- the recent market prices of, and demand for, publicly traded shares of generally comparable companies; and
- other factors deemed relevant by the underwriters and us.

Neither we nor the underwriters can assure investors that an active trading market will develop for our ADSs, or that the ADSs will trade in the public market at or above the initial public offering price.

Other relationships

Certain of the underwriters and their affiliates have provided in the past to us and our affiliates and may provide from time to time in the future certain commercial banking, financial advisory, investment banking and other services for us and such affiliates in the ordinary course of their business, for which they have received and may continue to receive customary fees and commissions. In addition, from time to time, certain of the underwriters and their affiliates may effect transactions for their own account or the account of customers, and hold on behalf of themselves or their customers, long or short positions in our debt or equity securities or loans, and may do so in the future. Such investment and trading activities may involve or relate to assets, securities and/or instruments of the issuer (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the issuer. The underwriters and their affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

Selling restrictions

General

Other than in the United States, no action has been taken by us or the underwriters that would permit a public offering of the securities offered by this prospectus in any jurisdiction where action for that purpose is required. The securities offered by this prospectus may not be offered or sold, directly or indirectly, nor may this prospectus or any other offering material or advertisements in connection with the offer and sale of any such securities be distributed or published in any jurisdiction, except under circumstances that will result in compliance with the applicable rules and regulations of that jurisdiction. Persons into whose possession this prospectus comes are advised to inform themselves about and to observe any restrictions relating to the offering and the distribution of this prospectus. This prospectus does not constitute an offer to sell or a solicitation of an offer to buy any securities offered by this prospectus in any jurisdiction in which such an offer or a solicitation is unlawful.

European economic area

In relation to each Member State of the EEA, or each, a Relevant Member State, no offer of ADSs may be made to the public in that Relevant Member State other than:

- A. to any legal entity which is a qualified investor as defined in the Prospectus Directive;

- B. to fewer than 100 or, if the Relevant Member State has implemented the relevant provision of the 2010 PD Amending Directive, 150, natural or legal persons (other than qualified investors as defined in the Prospectus Directive), as permitted under the Prospectus Directive, subject to obtaining the prior consent of the representatives; or
- C. in any other circumstances falling within Article 3(2) of the Prospectus Directive,
provided that no such offer of ADSs shall require us or the representatives to publish a prospectus pursuant to Article 3 of the Prospectus Directive or supplement a prospectus pursuant to Article 16 of the Prospectus Directive.

Each person in a Relevant Member State who initially acquires any ADSs or to whom any offer is made will be deemed to have represented, acknowledged and agreed that it is a “qualified investor” within the meaning of the law in that Relevant Member State implementing Article 2(1)(e) of the Prospectus Directive. In the case of any ADSs being offered to a financial intermediary as that term is used in Article 3(2) of the Prospectus Directive, each such financial intermediary will be deemed to have represented, acknowledged and agreed that the ADSs acquired by it in the offer have not been acquired on a non-discretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in circumstances which may give rise to an offer of any ADSs to the public other than their offer or resale in a Relevant Member State to qualified investors as so defined or in circumstances in which the prior consent of the representatives has been obtained to each such proposed offer or resale.

The Company, the representatives and their affiliates will rely upon the truth and accuracy of the foregoing representations, acknowledgements and agreements.

This prospectus has been prepared on the basis that any offer of ADSs in any Relevant Member State will be made pursuant to an exemption under the Prospectus Directive from the requirement to publish a prospectus for offers of ADSs. Accordingly any person making or intending to make an offer in that Relevant Member State of ADSs which are the subject of the offering contemplated in this prospectus may only do so in circumstances in which no obligation arises for the Company or any of the underwriters to publish a prospectus pursuant to Article 3 of the Prospectus Directive in relation to such offer. Neither the Company nor the underwriters have authorized, nor do they authorize, the making of any offer of ADSs in circumstances in which an obligation arises for the Company or the underwriters to publish a prospectus for such offer.

For the purpose of the above provisions, the expression “an offer to the public” in relation to any ADSs in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and the ADSs to be offered so as to enable an investor to decide to purchase or subscribe the ADSs, as the same may be varied in the Relevant Member State by any measure implementing the Prospectus Directive in the Relevant Member State and the expression “Prospectus Directive” means Directive 2003/71/EC (including the 2010 PD Amending Directive, to the extent implemented in the Relevant Member States) and includes any relevant implementing measure in the Relevant Member State and the expression “2010 PD Amending Directive” means Directive 2010/73/EU.

Hong Kong

The ADSs may not be offered or sold by means of any document other than (i) in circumstances that do not constitute an offer to the public within the meaning of the Companies Ordinance (Cap.32, Laws of Hong Kong), or (ii) to “professional investors” within the meaning of the

[Table of Contents](#)

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 Select Market listing fee and the filing fee payable to FINRA, all amounts are estimates.

Expense	Amount
SEC registration fee	\$ 31,594
Nasdaq Global Select Market listing fee	225,000
FINRA filing fee	37,300
Underwriters legal fees	45,000
Printing expenses	350,000
Legal fees and expenses	2,000,000
Accounting fees and expenses	1,200,000
Miscellaneous costs	261,106
Total	\$ 4,150,000

Legal matters

The validity of our ADSs and certain other matters of English law and U.S. federal law will be passed upon for us by Goodwin Procter (UK) LLP and Goodwin Procter LLP. Legal counsel to the underwriters in connection with this offering are Davis Polk & Wardwell LLP.

Experts

The consolidated financial statements of Orchard Therapeutics Limited as of December 31, 2016 and December 31, 2017 and for each of the two years in the period ended December 31, 2017 included in this prospectus have been so included in reliance on the report of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

The registered business address of PricewaterhouseCoopers LLP is 1 Embankment Place, London, WC2N 6RH, United Kingdom.

Service of process and enforcement of liabilities

We are incorporated and currently existing under the laws of England and Wales. In addition, certain of our directors and officers reside outside of the United States and most of the assets of our non-U.S. subsidiaries are located outside of the United States. As a result, it may be difficult for investors to effect service of process on us or those persons in the United States or to enforce in the United States judgments obtained in United States courts against us or those persons based on the civil liability or other provisions of the United States securities laws or other laws.

In addition, uncertainty exists as to whether the courts of England and Wales would:

- recognize or enforce judgments of United States courts obtained against us or our directors or officers predicated upon the civil liabilities provisions of the securities laws of the United States or any state in the United States; or
- entertain original actions brought in England and Wales against us or our directors or officers predicated upon the securities laws of the United States or any state in the United States.

We have been advised by Goodwin Procter LLP that there is currently no treaty between (i) the United States and (ii) England and Wales providing for reciprocal recognition and enforcement of judgments of United States courts in civil and commercial matters (although the United States and the United Kingdom are both parties to the New York Convention on the Recognition and Enforcement of Foreign Arbitral Awards) and that a final judgment for the payment of money rendered by any general or state court in the United States based on civil liability, whether predicated solely upon the United States securities laws, would not be automatically enforceable in England and Wales. We have also been advised by Goodwin Procter LLP that any final and conclusive monetary judgment for a definite sum obtained against us in United States courts would be treated by the courts of England and Wales as a cause of action in itself and sued upon as a debt at common law so that no retrial of the issues would be necessary, provided that:

- the relevant U.S. court had jurisdiction over the original proceedings according to English conflicts of laws principles at the time when proceedings were initiated;
- England and Wales courts had jurisdiction over the matter on enforcement and we either submitted to such jurisdiction or were resident or carrying on business within such jurisdiction and were duly served with process;
- the U.S. judgment was final and conclusive on the merits in the sense of being final and unalterable in the court that pronounced it and being for a definite sum of money;
- the judgment given by the courts was not in respect of penalties, taxes, fines or similar fiscal or revenue obligations (or otherwise based on a U.S. law that an English court considers to relate to a penal, revenue or other public law);
- the judgment was not procured by fraud;
- recognition or enforcement of the judgment in England and Wales would not be contrary to public policy or the Human Rights Act 1998;
- the proceedings pursuant to which judgment was obtained were not contrary to natural justice;
- the U.S. judgment was not arrived at by doubling, trebling or otherwise multiplying a sum assessed as compensation for the loss or damages sustained and not being otherwise in breach

[Table of Contents](#)

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
Index to Financial Statements as of December 31, 2016 and 2017 and for the Years Ended December 31, 2016 and 2017	
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
Index to Unaudited Interim Condensed Financial Statements as of December 31, 2017 and June 30, 2018 (as restated) and for the Six Month Periods Ended June 30, 2017 and 2018 (as restated)	
Condensed consolidated balance sheets	F-44
Condensed consolidated statements of operations and comprehensive loss	F-45
Condensed consolidated statements of shareholders' equity	F-46
Condensed consolidated statements of cash flows	F-47
Notes to condensed consolidated financial statements	F-48

All historical share and per share data included in these financial statements exclude the impact of the 1-for-0.8003 reverse share split that will be part of our corporate reorganization. The pro forma earnings per share data does give effect to the split.

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Orchard Therapeutics Limited

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Orchard Therapeutics Limited and its subsidiaries as of December 31, 2017 and 2016, and the related consolidated statements of operations and comprehensive loss, of convertible preferred shares and shareholders' (deficit) equity and of cash flows for each of the two years in the period ended December 31, 2017, including the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2017 and 2016, and the results of their operations and their cash flows for each of the two years in the period ended December 31, 2017 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's consolidated financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) ("PCAOB") and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits of these consolidated financial statements in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the consolidated financial statements are free of material misstatement, whether due to error or fraud.

Our audits included performing procedures to assess the risks of material misstatement of the consolidated financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the consolidated financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP

PricewaterhouseCoopers LLP

Reading, United Kingdom

August 6, 2018, except for the effects of the revision discussed in Note 14 to the consolidated financial statements, as to which the date is October 23, 2018

We have served as the Company's auditor since 2018.

Orchard Therapeutics Limited

Consolidated balance sheets

(In thousands, except share and per share amounts)

	December 31	
	2016	2017
Assets		
Current assets:		
Cash	\$ 3,497	\$ 89,856
Other receivables	33	1,247
Prepaid expenses and other current assets	448	3,118
Total current assets	3,978	94,221
Non-current assets:		
Property and equipment, net	184	2,713
Other long-term receivables	121	360
Total non-current assets	305	3,073
Total assets	\$ 4,283	\$ 97,294
Liabilities, convertible preferred shares and shareholders' (deficit) equity		
Current liabilities:		
Accounts payable	\$ 698	\$ 3,891
Accrued expenses and other current liabilities	1,715	6,864
Tranche obligations	1,402	—
Total current liabilities	3,815	10,755
Other long-term liabilities	22	134
Total liabilities	3,837	10,889
Commitments and contingencies (<i>Note 11</i>)		
Convertible preferred shares: £0.00001 par value; 21,000,000 shares authorized as of December 31, 2016; 14,000,000 shares issued and outstanding as of December 31, 2016; aggregate liquidation preference of \$17,222 as of December 31, 2016.		
	16,970	—
Shareholders' (deficit) equity:		
Convertible preferred shares, £0.00001 par value; 42,198,154 shares authorized as of December 31, 2017; 41,581,513 shares issued and outstanding as of December 31, 2017; aggregate liquidation preference of \$139,954 as of December 31, 2017.		
	—	134,069
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,000 and £675,413 of shares at December 31, 2016 and 2017, respectively; 9,305,175 and 11,154,720 shares issued and outstanding at December 31, 2016 and 2017, respectively.		
	—	—
Additional paid-in capital	3,404	7,610
Accumulated other comprehensive (loss) income	(271)	4,127
Accumulated deficit	(19,657)	(59,401)
Total shareholders' (deficit) equity	(16,524)	86,405
Total liabilities, convertible preferred shares and shareholders' (deficit) equity	\$ 4,283	\$ 97,294

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited

Consolidated statements of operations and comprehensive loss

(In thousands, except share and per share amounts)

	Year ended December 31,	
	2016	2017
Operating expenses:		
Research and development	\$ 16,206	\$ 32,527
General and administrative	2,997	5,985
Total operating expenses	19,203	38,512
Loss from operations	(19,203)	(38,512)
Other income (expense):		
Interest income	3	—
Change in fair value of tranche obligations	289	—
Other expense	(154)	(1,179)
Total other income (expense), net	138	(1,179)
Net loss before income tax	(19,065)	(39,691)
Income tax expense	(20)	(53)
Net loss attributable to ordinary shareholders	\$ (19,085)	\$ (39,744)
Other comprehensive (loss) income		
Foreign currency translation adjustment	(271)	4,398
Total comprehensive loss	\$ (19,356)	\$ (35,346)
Net loss per share attributable to ordinary shareholders, basic and diluted	\$ (2.15)	\$ (3.58)
Weighted average number of ordinary shares outstanding, basic and diluted	8,872,333	11,086,808
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	\$ (2.69)	\$ (4.48)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	7,100,528	8,872,768
Supplemental pro forma net loss per share attributable to ordinary shares, basic and diluted (unaudited)		\$ (1.24)
Supplemental pro forma weighted average number of ordinary shares outstanding, basis and diluted (unaudited)		32,056,206

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited

Consolidated statement of convertible preferred shares and shareholders' (deficit) equity

(In thousands, except share amounts)

	Convertible preferred shares		Convertible preferred shares		Ordinary shares		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
	Shares	Amount	Shares	Amount	Shares	Amount				
Balance at December 31, 2015	—	\$ —	—	\$ —	3,370,175	\$ —	\$ —	\$ —	\$ (572)	\$ (572)
Issuance of convertible preferred shares, net of issuance costs	14,000,000	16,970	—	—	—	—	—	—	—	—
Conversion of ordinary shares to deferred shares	—	—	—	(100,000)	—	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	204	—	—	204
Ordinary shares committed to be issued as part of license agreements	—	—	—	—	—	—	465	—	—	465
Ordinary shares issued as part of license agreements	—	—	—	—	6,035,000	—	2,735	—	—	2,735
Foreign currency translation adjustment	—	—	—	—	—	—	—	(271)	—	(271)
Net loss	—	—	—	—	—	—	—	—	(19,085)	(19,085)
Balance at December 31, 2016	14,000,000	\$ 16,970	—	\$ —	9,305,175	\$ —	\$ 3,404	\$ (271)	\$ (19,657)	\$ (16,524)
Issuance of convertible preferred shares, net of issuance costs	18,359,625	66,981	—	—	—	—	—	—	—	—
Reclassification of convertible preferred shares from temporary equity to permanent equity	(32,359,625)	(83,951)	32,359,625	83,951	—	—	—	—	—	83,951
Issuance of convertible preferred shares, net of issuance costs	—	—	9,221,888	50,118	—	—	—	—	—	50,118
Share-based compensation expense	—	—	—	—	—	—	1,019	—	—	1,019
Ordinary shares committed to be issued as part of license agreements	—	—	—	—	—	—	1,534	—	—	1,534
Ordinary shares issued as part of license agreements	—	—	—	—	1,849,545	—	1,653	—	—	1,653
Foreign currency translation adjustment	—	—	—	—	—	—	—	4,398	—	4,398
Net loss	—	—	—	—	—	—	—	—	(39,744)	(39,744)
Balance at December 31, 2017	—	\$ —	41,581,513	\$ 134,069	11,154,720	\$ —	\$ 7,610	\$ 4,127	\$ (59,401)	\$ 86,405

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited

Consolidated statements of cash flows

(In thousands, except share amounts)

	Year ended December 31,	
	2016	2017
Cash flows from operating activities		
Net loss	\$ (19,085)	\$ (39,744)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	6	302
Share-based compensation	204	1,019
Non-cash consideration for licenses	3,089	3,126
Change in fair value of tranche obligation liability	(289)	—
Changes in components of operating assets and liabilities:		
Other receivables	—	(1,168)
Prepaid and other assets	(639)	(2,737)
Accounts payable	666	1,930
Accrued expenses and other current liabilities	1,460	4,672
Other long-term liabilities	22	113
Net cash used in operating activities	(14,566)	(32,487)
Cash flows from investing activities		
Purchases of property and equipment	(190)	(1,559)
Net cash used in investing activities	(190)	(1,559)
Cash flows from financing activities		
Proceeds from the issuance of convertible preferred shares, net of issuance costs	18,034	115,696
Net cash provided by financing activities	18,034	115,696
Effect of exchange rate changes on cash	(751)	4,709
Net increase in cash	2,527	86,359
Cash—beginning of year	970	3,497
Cash—end of year	\$ 3,497	\$ 89,856
Supplemental disclosure of non-cash investing and financing activities		
Conversion of promissory note to convertible preferred shares	\$ 946	\$ —
Issuance of tranche obligations with convertible preferred shares	2,459	—
Settlement of tranche obligations	451	1,402
Property and equipment included in accrued expenses and accounts payable at period end	\$ —	\$ 1,247

See accompanying notes to consolidated financial statements.

Orchard Therapeutics Limited

Notes to consolidated financial statements

Years ended December 31, 2016 and 2017

(amounts in thousands, except share and per share data)

1. Nature of business and basis of presentation

Orchard Therapeutics Limited (the “Company”), a limited company incorporated pursuant to the laws of England and Wales in September 2015, is a commercial-stage fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. The Company’s gene therapy approach seeks to transform a patient’s own, or autologous, hematopoietic stem cells (HSCs) into a gene-modified drug product to treat the patient’s disease through a single administration.

The Company has acquired and developed a portfolio of autologous *ex vivo* gene therapies focused on three franchises in which it accumulates expertise, including primary immune deficiencies, inherited metabolic disorders and hemoglobinopathies. The Company’s programs include Strimvelis, the first autologous *ex vivo* gene therapy approved by the EMA for ADA-SCID, three clinical programs in advanced registrational studies in metachromatic leukodystrophy (“MLD”), Wiskott–Aldrich syndrome (“WAS”) and adenosine deaminase severe combined immunodeficiency (“ADA-SCID”), other clinical programs in X-linked chronic granulomatous disease (“X-CGD”) and transfusion-dependent beta-thalassemia (“TDBT”), as well as an extensive preclinical pipeline.

The Company is subject to risks and uncertainties common to early-stage companies in the biotechnology industry. There can be no assurance that the Company’s research and development will be successfully completed, that adequate protection for the Company’s technology will be obtained, that any products developed will obtain necessary government regulatory approval or that any products, if approved, will be commercially viable. The Company operates in an environment of rapid technological innovation and substantial competition from pharmaceutical and biotechnological companies. In addition, the Company is dependent upon the services of its employees, consultants and service providers. Even if the Company’s product development efforts are successful, it is uncertain when, if ever, the Company will realize significant revenue from product sales.

Through December 31, 2017, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares. The Company has incurred recurring losses since its inception, including net losses of \$19.1 million and \$39.7 million for the years ended December 31, 2016 and 2017, respectively. As of December 31, 2017, the Company had an accumulated deficit of \$59.4 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expected that its cash on hand as of December 31, 2017 of \$89.9 million, together with the approximately \$150.0 of gross cash proceeds received from the Company’s sale of Series C convertible preferred shares in August 2018 (Note 14) will be sufficient to fund its operations and capital expenditure requirements through at least 12 months from the issuance date of these consolidated financial statements.

The Company is seeking to complete an initial public offering (“IPO”) of American Depositary Shares (“ADSs”) each representing an ordinary share of the Company. In the event the Company

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

does not complete an IPO, the Company expects to seek additional funding through private equity financings, debt financings, or other capital sources, including collaborations with other companies, government contracts or other strategic transactions. The Company may not be able to obtain funding on acceptable terms, or at all, because the terms of any financing may adversely affect the holdings or the rights of the Company's shareholders.

If the Company is unable to obtain funding, the Company will be forced to delay, reduce or eliminate some or all of its research and development programs, product portfolio expansion or commercialization efforts, which could adversely affect its business prospects, or the Company may be unable to continue operations. Although management continues to pursue these plans, there is no assurance that the Company will be successful in obtaining sufficient funding on terms acceptable to the Company to fund continuing operations, if at all.

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company and its wholly owned subsidiary, Orchard Therapeutics North America, after elimination of all intercompany accounts and transactions.

2. Summary of significant accounting policies

Use of estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the fair values of ordinary and convertible preferred shares, the fair value of tranche obligations, share-based compensation and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Unaudited pro forma information

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma information represents information for Orchard Therapeutics plc for the years ended December 31, 2016 and 2017.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Unaudited supplemental pro forma information

In the accompanying consolidated statements of operations and comprehensive loss, the unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2017 has been prepared to give effect to, upon closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2017 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

Concentration of credit risk

The Company has no significant off-balance sheet risk, such as foreign currency contracts, options contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and other receivables. Periodically, the Company maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

Foreign currency translation

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

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Cash and cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at acquisition to be cash equivalents. In 2016 and 2017, the Company did not have any cash equivalents.

Property and equipment

Property and equipment are recorded at cost and depreciated or amortized using the straight-line method over the following estimated useful lives.

Property and equipment:	Estimated useful life
Lab equipment	5-10 years
Leasehold improvements	Shorter of lease term or estimated useful life
Furniture and fixtures	4 years
Office and computer equipment	3-5 years

As of December 31, 2016 and 2017, the Company's property and equipment consisted of furniture and fixtures, office and computer equipment, lab equipment and leasehold improvements. Upon retirement or sale, the cost of assets disposed of and the related accumulated depreciation are removed from the accounts, and any resulting gain or loss is included in the statement of operations and other comprehensive loss. Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred.

Impairment of long-lived assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, as determined in accordance with the related accounting literature. To date, the Company has not recorded any impairment losses on long-lived assets.

Fair value measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

(an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying values of the Company's other receivable, accounts payable, accrued expenses and other current liabilities approximate their fair values due to the short-term nature of these assets and liabilities.

Tranche obligations

In 2016, Series A convertible preferred shares (the "Series A convertible preferred shares") were issued in three tranches. The Company was obligated to issue second and third tranches of Series A convertible preferred shares once certain business milestones were met; these tranches were recognized as tranche obligations, which are subject to revaluation at each balance sheet date. Changes in fair value were recorded as a component of other income (expense) until the settlement of the tranche obligation.

The fair values of the tranche obligations are based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The tranche obligations are valued as a forward contract, and the values are determined using a probability-weighted present value calculation. In determining the fair values of the tranche obligations, estimates and assumptions impacting fair value included the fair value of the Company's convertible preferred shares, risk-free interest rates, the probability and estimated timing of the tranche closings, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares. The Company determines the per share fair value of the underlying convertible preferred shares using the option pricing model ("OPM"), which considers the preferred share price paid by

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

investors, the time to liquidity and volatility. In the OPM, the timing of the liquidity event determines the assumed life in the Black-Scholes calculation. The Company estimates a time to liquidity taking into account the future tranche funding. If the future tranche is not expected to be funded, a liquidity event will be assumed to have occurred. If the tranche is expected to be funded, a longer-term liquidity event is assumed to have occurred. Volatility is estimated based on the daily trading histories of comparable public companies. The risk-free interest rate is determined by reference to the United States Treasury yield curve. The Company estimated a 0% dividend yield based on the expected dividend yield and the fact that it has never paid or declared dividend.

Segment information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision maker in deciding how to allocate resources and assess performance. The Company and the Company's chief operating decision maker, the Company's Chief Executive Officer, views the Company's operations and manages its business as a single operating segment, which is focused on discovering, acquiring, developing and commercializing gene therapies for patients with rare disorders. The Company operates in two geographic regions: the United Kingdom and United States. The Company had fixed assets of \$0.5 million and \$2.2 million located in the United Kingdom and United States, respectively, as of December 31, 2017.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, facilities costs, depreciation, third-party license fees, and external costs of outside vendors engaged to conduct clinical development activities and clinical trials, as well as to manufacture clinical trial materials. Non-refundable prepayments for goods or services that will be used or rendered for future research and development activities are recorded as prepaid expenses. Such amounts are recognized as an expense as the goods are delivered or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered.

Research contract costs and accruals

The Company has entered into various research and development-related contracts. These agreements are cancelable, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Share-based compensation

The Company measures share-based awards granted to employees and directors based on the fair value on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, the Company issues share-based awards with only service-based vesting conditions and records the expense for these awards using the straight-line method. The Company has not issued any share-based awards with performance-based vesting conditions.

Prior to the adoption of Accounting Standards Update (“ASU”) No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting* (“ASU 2018-07”), which is discussed below under “Recently adopted accounting pronouncements,” the measurement date for non-employee awards was generally the date the services were completed, resulting in financial reporting period adjustments to share-based compensation during the vesting terms for changes in the fair value of the awards. At the end of each financial reporting period prior to completion of the service period, the fair value of the unvested awards was remeasured using the then-current fair value of the Company’s ordinary shares and updated assumption inputs in the Black-Scholes option-pricing model.

After adoption of ASU 2018-07, the measurement date for non-employee awards is the date of the grant. The compensation expense for non-employees is recognized, without changes in the fair value of the award, over the requisite service period, which is the vesting period of the respective award.

The Company classifies share-based compensation expense in its consolidated statement of operations and comprehensive loss in the same manner in which the award recipient’s payroll costs are classified or in which the award recipient’s service payments are classified.

The fair value of each option is estimated on the date of grant using the Black-Scholes option pricing model. Given the absence of an active market for the Company’s ordinary shares, the board of directors, the members of which the Company believes have extensive business, finance, and venture capital experience, was required to estimate the fair value of the Company’s ordinary share at the time of each grant of a share-based award. The board of directors determined the estimated fair value of the Company’s equity instruments based on a number of objective and subjective factors, including external market conditions affecting the biotechnology industry sector. The Company and the board of directors utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants’ Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require the Company’s judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of the Company’s ordinary shares at each grant date, including the following factors: (1) prices paid for the Company’s convertible preferred shares, which the Company had sold to outside investors in arm’s-length transactions, and the rights, preferences, and privileges of the Company’s convertible preferred shares and ordinary shares; (2) valuations performed by an independent valuation specialist; (3) the Company’s stage of development; (4) the fact that the grants of share-based awards involved illiquid securities in a private company; and (5) the likelihood of

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

achieving a liquidity event for the ordinary shares underlying the share-based awards, such as an IPO or sale of the Company, given prevailing market conditions.

Ordinary share valuations were prepared using the OPM to estimate the Company's enterprise value. The OPM treats ordinary and convertible preferred shares as call options on the total equity value of a company, with exercise prices based on the value thresholds at which the allocation among the various holders of a company's securities changes. Under this method, the ordinary shares have value only if the funds available for distribution to shareholders exceeded the value of the convertible preferred shares liquidation preferences at the time of the liquidity event, such as a strategic sale or a merger. A discount for lack of marketability of the ordinary shares is then applied to arrive at an indication of value for the ordinary shares. The hybrid method is a probability weighted expected return method, PWERM, where the equity value in one or more scenarios is calculated using an OPM. The PWERM is a scenario-based methodology that estimates the fair value of ordinary shares based upon an analysis of future values for the company, assuming various outcomes. The ordinary shares' value is based on the probability-weighted present value of expected future investment returns considering each of the possible outcomes available as well as the rights of each share class. The future value of the ordinary shares under each outcome is discounted back to the valuation date at an appropriate risk-adjusted discount rate and probability weighted to arrive at an indication of value for the ordinary shares.

The Company estimates its expected share price volatility based on the historical volatility of publicly traded peer companies and expects to continue to do so until it has adequate historical data regarding the volatility of its own traded share price.

The expected term of the Company's share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the United States Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the Company's history of not paying cash dividends on ordinary shares. The Company does not expect to pay any cash dividends in the foreseeable future.

Comprehensive loss

Comprehensive loss includes net loss as well as other changes in shareholders' equity (deficit) that result from transactions and economic events other than those with shareholders. For the years ended December 31, 2016 and 2017, comprehensive (loss) income included a loss of \$0.3 million and a gain of \$4.4 million, respectively, related to foreign currency translation adjustments.

Income tax credit

As a company that carries out extensive research and development activities, the Company seeks to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program ("SME Program") and the Research and Development Expenditure program ("RDEC Program"). Qualifying expenditures largely comprise

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income. Such credits are accounted as reductions in research and development expense in the period in which the expenditures were incurred.

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

The RDEC credits are not dependent on the Company generating future taxable income or on the ongoing tax status or tax position of the Company. As such the Company has recorded United Kingdom research and development tax credit as an offset to research and development expense in the consolidated statements of operations and comprehensive loss of \$0.2 million and \$0.7 million for the years ended December 31, 2016 and 2017, respectively. As of December 31, 2016, and 2017, the Company's tax incentive receivable from the United Kingdom government was \$0.1 million and \$0.9 million, respectively. These amounts have not yet been paid to the Company by HMRC.

Income taxes

The Company is subject to United Kingdom corporate taxation. Due to the nature of its business, the Company has generated losses since inception and has therefore not paid United Kingdom corporation tax. The Company's income tax credit recognized represents the sum of the research and development tax credits recoverable in the United Kingdom and income tax payable in the United States.

Unsurrendered United Kingdom losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of United Kingdom taxable profits.

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

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred tax assets and liabilities are determined on the basis of the differences between the consolidated financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

that its deferred tax assets will be recovered in the future and, to the extent the Company believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company is subject to corporation taxes in the United Kingdom and the United States. The calculation of the Company's tax provision involves the application of both United Kingdom or United States tax law and requires judgement and estimates.

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

Net income (loss) per share

The Company follows the two-class method when computing net income (loss) per share as the Company has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of ordinary and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to ordinary shareholders for the period to be allocated between ordinary and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to ordinary shareholders is computed by dividing the net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period. Diluted net income (loss) attributable to ordinary shareholders is computed by adjusting net income (loss) attributable to ordinary shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to ordinary shareholders is computed by dividing the diluted net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares. For purpose of this calculation, outstanding options and convertible preferred shares are considered potential dilutive ordinary shares.

The Company's convertible preferred shares contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss attributable to ordinary shareholders, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to ordinary

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive. The Company reported a net loss attributable to ordinary shareholders for the years ended December 31, 2016 and 2017.

Recently adopted accounting pronouncements

In June 2018, the Financial Accounting Standards Board (“FASB”) issued ASU No. 2018-07 (“ASU 2018-07”). ASU 2018-07 expands the scope of Topic 718, *Compensation—Stock Compensation*, to include share-based payments issued to nonemployees for goods or services. Consequently, the accounting for share-based payments to nonemployees and employees will be substantially aligned. ASU 2018-07 supersedes Subtopic 505-50, *Equity—Equity-Based Payments to Non-Employees*. The amendments are effective for public companies for fiscal years beginning after December 15, 2018, including interim periods within that fiscal year. For all other companies, the amendments are effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted, but no earlier than a company’s adoption date of Topic 606. ASU 2018-07 was adopted as of January 1, 2017 and did not have a material impact on the Company’s financial position, results of operations or cash flows. The adoption will impact the value at which share-based payments to nonemployees is recognized.

In January 2017, the FASB issued ASU No. 2017-01, *Business Combinations (Topic 805) Clarifying the Definition of a Business* (“ASU 2017-01”). ASU 2017-01 clarifies the definition of a business by adding guidance to assist entities in evaluating whether transactions should be accounted for as acquisitions of assets or businesses. The definition of a business affects many areas of accounting including acquisitions, disposals, goodwill and consolidation. The ASU is effective for public entities for fiscal years beginning after December 15, 2017. For all other entities, the guidance is effective for annual periods beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early application is permitted for transactions for which the acquisition date occurs before the effective date when the transaction has not been reported in financial statements that have been issued or made available for issuance. As such, the Company adopted this standard effective as of January 1, 2016 and applied it to its arrangements entered into during the years ended December 31, 2016 and 2017 (Note 8).

In March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* (“ASU 2016-09”). ASU 2016-09 addresses several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross share compensation expense with actual forfeitures recognized as they occur, and classification on the statement of cash flows. Certain of these changes are required to be applied retrospectively, while other changes are required to be applied prospectively. ASU 2016-09 is effective for public entities for annual periods beginning after December 15, 2016, and interim periods within those annual periods. For all other entities, the guidance is effective for annual periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2018. Early adoption is permitted for any entity in any interim or

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

annual period and an entity that elects early adoption must adopt all of the amendments in the same period. The Company early adopted ASU 2016-09 effective as of January 1, 2016. The adoption of ASU 2016-09 did not have a material impact on the Company's financial position, results of operations or cash flows.

In November 2015, the FASB issued ASU No. 2015-17, *Income Taxes (Topic 740): Balance Sheet Classification of Deferred Taxes* ("ASU 2015-17"), which requires deferred tax liabilities and assets to be classified as non-current in the consolidated balance sheet. ASU 2015-17 is effective for public entities for annual periods beginning after December 15, 2016, and interim periods within those annual periods. For all other entities, the guidance is effective for annual periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2018. Early adoption is permitted and the Company elected to early adopt the standard on January 1, 2016. The adoption of ASU 2015-17 had no material impact on the Company's financial position, results of operations or cash flows.

In November 2014, the FASB issued ASU No. 2014-16, *Determining Whether the Host Contract in a Hybrid Financial Instrument Issued in the Form of a Share Is More Akin to Debt or to Equity* ("ASU 2014-16"). The guidance requires an entity to determine the nature of the host contract by considering all stated and implied substantive terms and features of the hybrid financial instrument, weighing each term and feature on the basis of the relevant facts and circumstances (commonly referred to as the whole-instrument approach). The Company adopted the standard modified retrospectively to all periods presented on the required effective date of January 1, 2016, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In August 2014, the FASB issued ASU No. 2014-15, *Disclosure of Uncertainties about an Entity's Ability to Continue as a Going Concern* ("ASU 2014-15"). The amendments in this update explicitly require a company's management to assess an entity's ability to continue as a going concern and to provide related footnote disclosures in certain circumstances. The new standard is effective for all entities for annual periods ending after December 15, 2016 and for annual and interim periods thereafter. Early adoption is permitted. The Company adopted ASU 2014-15 as of the required effective date of December 31, 2016. This guidance relates to footnote disclosure only, and its adoption had no impact on the Company's financial position, results of operations or cash flows.

In May 2014, the FASB issued ASU No. 2014-09, *Revenue from Contracts with Customers (Topic 606)* ("ASU 2014-09"), which supersedes existing revenue recognition guidance under GAAP. The standard's core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods or services. The standard defines a five-step process to achieve this principle and will require companies to use more judgment and make more estimates than under the current guidance. The Company expects that these judgments and estimates will include identifying performance obligations in the customer contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

cash flows arising from customer contracts. In August 2015, the FASB issued ASU 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, which delays the effective date of ASU 2014-09 such that the standard is effective for public entities for annual period beginning after December 15, 2017, including interim periods within those fiscal years. For all other entities, the guidance is effective beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early adoption of the standard is permitted for annual periods beginning after December 15, 2016, including interim periods within those fiscal years. The Company adopted these revenue standards on January 1, 2017. In 2016 and 2017, the Company did not have any revenue.

Recently issued accounting pronouncements

In March 2018, the FASB issued ASU No. 2018-05, *Income Taxes (Topic 740): Amendments to SEC Paragraphs Pursuant to SEC Staff Accounting Bulletin No. 118* ("ASU 2018-05"). ASU 2018-05 amends SEC paragraphs in ASC 740 to reflect SEC Staff Accounting Bulletin (SAB) No.118. When the 2017 Tax Cuts and Jobs Act (the "Act") was signed into law, the SEC staff released SAB 118 for applying Topic 740 as it relates to the Act. SAB 118 outlines the approach companies may take if they determine that the necessary information is not available (in reasonable detail) to evaluate, compute, and prepare accounting entries to recognize the effect(s) of the Act by the time the financial statements are required to be filed. Companies may use this approach when the timely determination of some or all of the income tax effect(s) from the Act is incomplete by the due date of the financial statements. SAB 118 also prescribes disclosures that reporting entities must provide in these circumstances. The amendments to the Accounting Standards Codification became effective upon issuance. The Company has conducted a preliminary assessment of its income tax effects of the Act. Additional analysis of the law and the impact to the Company may be performed, if needed, and any impact will be finalized no later than the fourth quarter of 2018.

In July 2017, the FASB issued ASU No. 2017-11, *Earnings Per Share (Topic 260), Distinguishing Liabilities from Equity (Topic 480), Derivatives and Hedging (Topic 815) (Part I) Accounting for Certain Financial Instruments with Down Round Features, (Part II) Replacement of the Indefinite Deferral for Mandatorily Redeemable Financial Instruments of Certain Nonpublic Entities and Certain Mandatorily Redeemable Noncontrolling Interests with a Scope Exception* ("ASU 2017-11"). Part I applies to entities that issue financial instruments such as warrants, convertible debt or convertible preferred stock that contain down-round features. Part II replaces the indefinite deferral for certain mandatorily redeemable noncontrolling interests and mandatorily redeemable financial instruments of nonpublic entities contained within ASC Topic 480 with a scope exception and does not impact the accounting for these mandatorily redeemable instruments. ASU 2017-11 is required to be adopted for public entities for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2018. For all other entities, the guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted for all entities. The Company is currently evaluating the impact that the adoption of ASU 2017-11 will have on its consolidated financial statements.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

In May 2017, the FASB issued ASU No. 2017-09, *Compensation—Stock Compensation (Topic 718): Scope of Modification Accounting* (“ASU 2017-09”), which clarifies when to account for a change to the terms or conditions of a share-based payment award as a modification. Under the new guidance, modification accounting is required only if the fair value, the vesting conditions or the classification of the award (as equity or liability) changes as a result of the change in terms or conditions. ASU 2017-09 is effective for all entities annual periods, and interim periods within those annual periods, beginning after December 15, 2017. Early adoption is permitted, including adoption in any interim period, for 1) public business entities for reporting periods for which financial statements have not yet been issued and 2) all other entities for reporting periods for which financial statements have not yet been made available for issuance. The Company will adopt ASU 2017-09 as of the required effective date of January 1, 2018. The adoption of ASU 2017-09 is expected to have an impact on the modification of share-based awards, if any, after the date of adoption. The adoption of ASU 2017-09 is not expected to have a material impact on the Company’s financial position, results of operations or cash flows.

In February 2016, the FASB issued ASU No. 2016-02, *Leases (Topic 842)* (“ASU 2016-02”), which sets out the principles for the recognition, measurement, presentation and disclosure of leases for both parties to a contract (i.e., lessees and lessors). The new standard requires lessees to apply a dual approach, classifying leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee. This classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than 12 months regardless of their classification. Leases with a term of 12 months or less will be accounted for similar to existing guidance for operating leases today. In January 2018, the FASB issued ASU 2018-01, *Leases (Topic 842)*, (“ASU 2018-01”), which adds two practical expedients to the new lease guidance. Topic 842 is effective for annual periods beginning after December 15, 2018, including interim periods within those fiscal years for public business entities, certain not-for-profit, and employee benefit plans that file with the SEC. For all other entities, the guidance is effective for fiscal years beginning after December 15, 2019, and interim periods within fiscal years beginning after December 15, 2020. Early adoption is permitted for all entities. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements.

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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following table presents information about the Company's financial liabilities that have been measured at fair value on a recurring basis as of December 31, 2016 (there were no financial liabilities measured at fair value on a recurring basis as of December 31, 2017):

	Fair value measurements as of December 31, 2016 using:			
	Level 1	Level 2	Level 3	Total
	(in thousands)			
Liabilities:				
Tranche obligations	\$ —	\$ —	\$ 1,402	\$1,402
	\$ —	\$ —	\$ 1,402	\$1,402

The tranche obligations in the table above represents the Company's obligation to issue for sale Series A convertible preferred shares once certain business milestones were met. The fair value of the tranche obligations was based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The tranche obligations are valued as a forward contract as described in Note 2. The Company assessed these assumptions and estimates on a quarterly basis as additional information impacting the assumptions was obtained. The Company recognized changes in fair value of these tranche obligations as a component of other income (expense) in its consolidated statement of operations and comprehensive loss.

Estimates and assumptions impacting the fair value measurement included the fair value of the Company's convertible preferred shares, risk-free interest rate, the probability and estimated timing of each tranche closings, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares (Note 2). Significant changes to the fair value of the underlying shares would have resulted in a significant change in the fair value measurements.

The tranche obligations were settled when the respective second and third tranches of Series A convertible preferred shares were issued in July 2016 and January 2017.

The following assumptions were used in valuing the tranche obligations:

	Year Ended December 31, 2016
Risk-free interest rate	0.00 - 0.53%
Expected dividend yield	0.00%
Expected term (in years)	0.00 - 0.92
Expected volatility	75.5 - 89.9%
Fair value of convertible preferred shares	\$ 1.00 - \$1.58

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following table provides a rollforward of the fair value of the tranche obligations measured at fair value on a recurring basis using Level 3 significant unobservable inputs:

	Tranche obligations	
	(in thousands)	
Balance at December 31, 2015	\$	—
Issuance of tranche obligations to purchase convertible preferred shares		2,459
Change in fair value of second tranche obligation		(424)
Settlement of second tranche obligation upon issuance of convertible preferred shares		(451)
Change in fair value of third tranche obligation		135
Effect of exchange rate changes on tranche obligation		(317)
Balance at December 31, 2016		1,402
Settlement of third tranche obligation upon issuance of convertible preferred shares		(1,402)
Balance at December 31, 2017	\$	—

4. Property and equipment

Property and equipment consist of the following:

	December 31,	
	2016	2017
	(in thousands)	
Property and equipment:		
Lab equipment	\$178	\$ 2,708
Leasehold improvements	—	244
Furniture and fixtures	12	59
Office and IT equipment	—	12
Property and equipment	190	3,023
Less: accumulated depreciation	(6)	(310)
Property and equipment, net	\$184	\$ 2,713

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

5. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2016	2017
	(in thousands)	
Accrued external research and development expenses	\$1,260	\$1,834
Accrued payroll and related expenses	244	2,090
Accrued professional fees	126	394
Accrued other	85	279
Deferred UCLA reimbursement	—	2,267
Total accrued expenses and other current liabilities	\$1,715	\$6,864

As of December 31, 2016, the Company did not have property and equipment that was received but not yet invoiced. As of December 31, 2017, accrued other includes \$0.1 million of lab equipment that was acquired and received but not yet invoiced.

6. Shareholders' equity and convertible preferred shares

Convertible preferred shares

As of December 31, 2016, the Company's Articles of Association (the "Articles") authorized a total of 21,000,000 convertible preferred shares with a par value of £0.00001 per share, all of which have been designated as Series A convertible preferred shares. As of December 31, 2017, the Articles, as further amended and restated (the "Amended Articles"), authorized a total of 42,198,154 convertible preferred shares with a par value of £0.00001 per share, of which 21,000,000 shares have been designated as Series A convertible preferred shares and 21,198,154 shares have been designated as Series B convertible preferred shares (the "Series B convertible preferred shares").

Until September 2017, the Series A and Series B convertible preferred shares (collectively, the "Convertible Preferred Shares") were classified in temporary equity as the Convertible Preferred Shares were contingently redeemable. A contingent redemption feature, which is at the option of the Company, could have been exercised by a holder of the Convertible Preferred Shares while that holder controlled a majority of the Company's board of directors. The Convertible Preferred Shares did not become redeemable as the contingency had not been met or determined to be probable.

In September 2017, the Company's board of directors was expanded so that the holder of the Convertible Preferred Shares no longer controlled the Company's board of directors through a majority of seats. Based on this change, the redemption feature from September 2017 onward is exercisable only in an event that is within the control of the Company. At that date, the Convertible Preferred Shares were reclassified to permanent equity within shareholders' equity on the Company's consolidated balance sheets.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

In December 2015, the Company issued unsecured convertible loan notes (“the Notes”) to an investor for principal amount of \$0.9 million. The first six months from date of the Note issuance were interest free. After six months, an interest rate of 3% per annum was charged and shall accrue monthly in arrears. In February 2016, as part of the issuance of the first tranche of Series A convertible preferred shares, the Notes of \$0.9 million were converted into 654,000 Series A convertible preferred shares at conversion price of £1.00.

Preferred share financings

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

In May 2016, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of \$0.4 million.

In July 2016, the Company issued and sold 6,666,667 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of \$8.7 million.

In August 2016, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of \$0.4 million.

In January 2017, the Company issued and sold 6,666,667 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of \$8.2 million.

In February 2017, the Company issued and sold 333,333 Series A convertible preferred shares at a price of £1.00 per share for net proceeds of \$0.4 million.

In March 2017, the Company issued and sold 7,254,000 Series B convertible preferred shares at a price of £4.019 per share (the “Series B Original Issue Price”) for net proceeds of \$36.0 million.

In August 2017, the Company issued and sold 4,105,625 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of \$21.0 million.

In October 2017, the Company issued and sold 5,817,801 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of \$30.8 million.

In December 2017, the Company issued and sold 3,404,087 Series B convertible preferred shares at a price of £4.019 per share for net proceeds of \$18.3 million.

In December 2017, the Company received proceeds of \$1.0 million for 188,313 Series B convertible preferred shares, which were subsequently issued in January 2018 (Note 14).

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

As of each balance sheet, the Convertible Preferred Shares consisted of the following:

	December 31, 2016				
	(in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	14,000,000	\$ 16,970	\$ 17,222	14,000,000
	21,000,000	14,000,000	\$ 16,970	\$ 17,222	14,000,000

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2016.

	December 31, 2017				
	(in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	\$ 26,994	\$ 28,337	21,000,000
Series B convertible preferred shares	21,198,154	20,581,513	107,075	111,617	20,581,513
	42,198,154	41,581,513	\$134,069	\$ 139,954	41,581,513

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2017.

The holders of the Convertible Preferred Shares have the following rights and preferences as of December 31, 2017:

Voting

Each Series A and Series B share shall confer one right to vote at all general meetings and to receive and vote on proposed written resolutions of the Company.

Conversion

Each Series A preferred share shall be convertible, at the option of the holder, at any time and from time to time, and without the payment of additional consideration, into an ordinary share as is determined by dividing the applicable Series A Original Issue Price by the Series A Conversion Price. Each Series B preferred share shall be convertible, at the option of the holder, at any time and from time to time, and without the payment of additional consideration, into an ordinary share as is determined by dividing the applicable Series B Original Issue Price by the Series B Conversion Price.

The Series A Conversion Prices were equal to each applicable Series A Original Issue Price as noted above. The Series B Conversion Prices were equal to each applicable Series B Original Issue Price as noted above. As of December 31, 2016 and 2017, each Preferred Share was convertible into one ordinary share.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

As set forth in the Amended Articles, the Series A and B Conversion Prices shall be adjusted when there is a deemed issuance of additional convertible preferred shares issued at a price lower than Series A and Series B Original Issue Prices or issuance of an instrument with rights that could dilute the interest of Series A and B holders. In addition, each Preferred Share will be automatically converted into an ordinary share at the applicable conversion ratio then in effect for each series of Convertible Preferred Shares upon the earlier of (i) the closing of a firm commitment underwritten public offering of its ordinary shares with gross proceeds to the Company of at least \$50.0 million and at a price per share of not less than £4.8228, subject to appropriate adjustment in the event of any share split, share dividend, combination or other similar recapitalization, or (ii) a date specified vote or written consent of the holders of a majority of Convertible Preferred Shares, voting together as a single class on an as-if-converted to ordinary shares basis.

Dividends

The holders of the Series A convertible preferred shares, Series B convertible preferred shares, and ordinary shares are entitled to receive non-cumulative dividends, if and when declared by the Company's board of directors, subject to shareholder consent. The Series A convertible preferred shares, Series B convertible preferred shares and ordinary shares rank equally in all respects (on an as converted basis) for the purpose of any dividend that is declared or paid. On a distribution of assets on a liquidation, share sale, asset sale or IPO, the holders of Series A convertible preferred shares, and Series B convertible preferred shares are entitled to receive any declared but unpaid dividend, in the order of the priority set out in Liquidation Preference below, on each outstanding Series A convertible preferred share and Series B convertible preferred share. No dividends were declared or paid during the years ended December 31, 2016 or 2017.

Liquidation preference

In the event of a distribution of assets on liquidation or a return of capital (other than a conversion, redemption or purchase of shares), the surplus remaining after settling the Company's assets and liabilities will be distributed to the individuals holding ordinary shares, Series A and Series B convertible preferred shares on a pro rata basis (as if the ordinary shares and the Convertible Preferred Shares constituted one class) as described in the Amended Articles, except if the per share amount for Series A and Series B convertible preferred shares results in a price per share less than its original issue price. If the price per share is less than the original issue price for preferred shareholders, the shareholders will be paid an amount equal to the subscription price and the remainder of the assets will be distributed on a pro rata basis to the remaining ordinary shareholders.

Redemption

The Amended Articles do not provide redemption rights to the holders of Convertible Preferred Shares.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Ordinary shares

The voting, dividend and liquidation rights of the holders of the Company's ordinary shares are subject to and qualified by the rights, powers and preferences of the holders of the Convertible Preferred Shares set forth above. Each ordinary share entitles the holder to one vote, together with the holders of Convertible Preferred Shares, on all matters submitted to the shareholders for a vote. The holders of Convertible Preferred Shares are entitled to elect a total of three directors of the Company. The holders of ordinary shares are entitled to elect the remaining directors of the Company by vote of a majority of such shares. Ordinary shareholders are entitled to receive dividends, as may be declared by the board of directors, if any, subject to the Liquidation Preference priority noted above. Through December 31, 2017, no cash dividends have been declared or paid.

As of December 31, 2016, and 2017, the Company had authority to allot ordinary shares up to a maximum nominal value of £675,000 and £675,413, respectively, with a normal value of £0.00001 per share. The authority has taken into consideration the conversion of outstanding Convertible Preferred Shares of 14,000,000 and 41,581,513 as of December 31, 2016 and 2017, respectively; 1,113,000 and 625,511 ordinary shares the Company committed to issue as part of its license and research agreements as of December 31, 2016 and 2017, respectively; 2,260,966 and 5,223,443 for the exercise of outstanding share options, as of December 31, 2016 and 2017, respectively; and 5,904,618 and 2,942,141 shares remaining available for future issuance under the 2016 Share Option Plan as of December 31, 2016 and 2017, respectively.

Ordinary share issuances

In February 2016, and amended in July 2017, the Company entered into a license agreement (the "UCLB/UCLA License Agreement") with UCL Business PLC ("UCLB"), which is the commercialization company of University College London, and The Regents of the University of California ("UCLA") (Note 8), pursuant to which the Company issued 4,300,000 and 1,529,545 ordinary shares in 2016 and 2017, respectively, to UCLB. The shares were recorded at their fair values as of the time the agreement was executed or modified, which was an aggregate of \$3.8 million. Amounts totaling \$2.1 million and \$1.7 million were recorded to research and development expense for the years ended December 31, 2016 and 2017, respectively.

In November 2016, the Company entered into a license and development agreement with Oxford BioMedica U.K. Limited ("Oxford BioMedica") (Note 8). As consideration for the rights and licenses granted to Orchard under the license and development agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica in December 2016. The Company also agreed to grant additional ordinary shares upon achievement of specified milestones. In November 2017, the first milestone was achieved and the Company was obligated to issue an additional 188,462 shares. The shares issued in 2016 and 2017 were recorded based on their fair values as of the time the agreement was executed of \$0.5 million and \$0.1 million, respectively. The amounts were recorded to research and development expense in the years ended December 31, 2016 and 2017, respectively.

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

its programs. As part of the consideration related to these license agreement, the total share commitment was 1,288,000 and 469,049 ordinary shares in 2016 and 2017, respectively. Pursuant to these agreements, the Company issued 1,000,000 and 320,000 ordinary shares in 2016 and 2017, respectively. The share commitments were recorded to research and development expense based on their fair values as of the time the respective agreement was executed or modified. The amounts were \$0.5 million and \$1.4 million in 2016 and 2017, respectively.

As of December 31, 2016 and 2017, the Company had outstanding 9,305,175 and 11,154,720 ordinary shares, respectively.

Deferred shares

Deferred shares are a unit of equity in the Company. All deferred shares can be repurchased at any time by the Company at a purchase price of £0.00001 per share. Deferred shares have no rights attached to them, are not convertible to any other class of shares and are not redeemable. The entire class of deferred shares is entitled to a total of £1.00 from the distribution of assets on a liquidation or return of capital event.

In 2016, the Company converted 100,000 ordinary shares of an investor to deferred shares. In March 2017, the Company repurchased 100,000 deferred shares at £0.00001 per share and simultaneously cancelled them.

As of December 31, 2016, the Company had 100,000 deferred shares outstanding. There were no deferred shares outstanding as of December 31, 2017.

7. Share-based compensation

2016 Share option plan

In September 2016, the Company adopted the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"). The 2016 Plan provides for the Company to grant incentive and non-qualified options to officers, directors, consultants, and advisors to purchase the Company's ordinary shares.

The total number of ordinary shares that may be issued under the 2016 Plan was 8,165,584 shares as of December 31, 2017, of which 2,942,141 shares remained available for future grant.

The Company typically grants options to United States employees and non-employees at exercise prices deemed by the board of directors to be equal to the fair value of the ordinary share at the time of grant and grant options to United Kingdom employees at an exercise price equal to the par value of the ordinary shares of £0.00001. The vesting period is determined by the board of directors, which is generally four years. An option's maximum term is ten years.

Shares that are expired, terminated, surrendered or canceled under the 2016 Plan without having been fully exercised will be available for future awards.

During the years ended December 31, 2016 and 2017, the Company granted options to purchase 1,507,763 and 3,039,235 ordinary shares, respectively, to employees and directors. The Company

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

recorded share-based compensation expense for options granted to employees and directors of \$0.1 million and \$0.9 million during the years ended December 31, 2016 and 2017, respectively.

In 2016, the Company granted options to purchase 753,203 ordinary shares to a non-employee. There were no options granted to non-employees during the year ended December 31, 2017. The Company recorded share-based compensation expense for options granted to the non-employee of \$0.1 million and \$0.2 million during the years ended December 31, 2016 and 2017, respectively.

Option valuation

When utilizing the Black-Scholes option-pricing model to determine the grant date fair value of share options granted to employees or the vesting or re-measurement date fair value for awards granted to non-employees in 2016, the Company used the following assumptions:

Employees and directors

	Year ended December 31,	
	2016	2017
Risk-free interest rate	1.52% - 2.20%	1.99% - 2.30%
Expected term (in years)	6.08	6.08
Expected volatility	77.80% - 78.50%	78.00% - 80.00%
Expected dividend rate	0.00%	0.00%

Non-employee

	Year ended December 31,	
	2016	2017
Risk-free interest rate	1.61% - 2.4%	1.52%
Expected term (in years)	9.75	6.08
Expected volatility	79.4% - 79.7%	77.80%
Expected dividend rate	0.00%	0.00%

Expected Term: The expected term for employees represents the period that the options granted are expected to be outstanding and is determined using the simplified method (based on the mid-point between the vesting date and the end of the contractual term). The expected term is applied to the share option grant group as a whole, as the Company does not expect substantially different exercise or post-vesting termination behavior among its employee population. Prior to the adoption of ASU 2018-07, expected term for non-employee grants was the contractual term of the options. After the adoption of ASU 2018-07, the expected term of share options granted to non-employees is determined in the same manner as share options granted to employees.

Expected Volatility: The Company used an average historical stock price volatility of comparable public companies within the biotechnology and pharmaceutical industry that were deemed to be representative of future share price trends as the Company does not have any trading history for its ordinary shares.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Risk-Free Interest Rate: The Company based the risk-free interest rate over the expected term of the options based on the constant maturity rate of United States Treasury securities with similar maturities as of the date of the grant.

Expected Dividend Rate: The Company has not paid and does not anticipate paying any dividends in the near future. Therefore, the expected dividend yield was zero.

Fair value of underlying ordinary shares: The Company determined the fair value of the underlying ordinary shares based on input from management and approved by the board of directors, as described in Note 2.

Options

The following table summarizes option activity under the 2016 Plan since December 31, 2016:

	Shares	Weighted average exercise price	Weighted average remaining contractual life	Aggregate intrinsic value
(in thousands, except share and per share amounts)				
Options outstanding at December 31, 2016	2,260,966	\$ 0.10	9.75	\$ 1,466
Granted	3,039,235	1.58		
Exercised	—	—		
Canceled	(76,758)	0.01	9.48	228
Options outstanding at December 31, 2017	<u>5,223,443</u>	0.96	9.28	10,483
Vested as of December 31, 2017	973,529	0.14	8.65	2,716

The weighted average exercise price of options granted to United Kingdom employees in 2017 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees 2017 was \$1.95.

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares.

The weighted average grant date fair value of the options granted during the years ended December 31, 2016 and 2017, was \$0.73 per share and \$2.16 per share, respectively.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Share-based compensation

Share-based compensation expense was classified in the consolidated statements of operations and comprehensive loss as follows:

	Year ended December 31,	
	2016	2017
		(in thousands)
Research and development	\$ 181	\$ 615
General and administrative	23	404
Total	\$ 204	\$ 1,019

The Company had 4,249,914 unvested options outstanding as of December 31, 2017. As of December 31, 2017, there was \$6.4 million of unrecognized compensation expense related to unvested options, that is expected to be recognized over a weighted average period of approximately 3.19 years.

8. License and research arrangements

UCLB/UCLA License Agreement

In February 2016, and amended in July 2017, the Company entered into the UCLB/UCLA License Agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of \$0.8 million for the license to the joint UCLB/UCLA technology and \$1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 5,829,545 ordinary shares to UCLB, of which 4,300,000 and 1,529,545 ordinary shares were issued in 2016 and 2017, respectively. The Company recorded research and development expense based on the fair value of the ordinary shares as of the time the agreement was executed or modified. The Company was also obligated to make an additional cash payment for clinical data. As of December 31, 2016, it had accrued \$0.6 million relating to the payment for clinical data in accrued expenses and other current liabilities on the consolidated balance sheet. In 2017, the Company paid \$0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

The Company recorded \$4.6 million and \$1.8 million of research and development costs, which comprise the upfront payments, issuance of ordinary shares and payments for clinical data, for the years ended December 31, 2016 and 2017, respectively.

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of \$0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company is obligated to make payments to the parties of up to an

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

aggregate of \$38.9 million upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

In connection with the UCLB/UCLA License Agreement, in February 2016 the Company sold an aggregate of 999,999 Series A convertible preferred shares at a price of £1.00 per share (Note 13).

Unless terminated earlier by either party, the UCLB/UCLA License Agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors for the Company ("Oxford BioMedica Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved and the Company was committed to issue 188,462 ordinary shares in 2018. As of December 31, 2017, the Company's remaining potential share obligation under the agreement comprised one milestone, which, upon achievement, would require the Company to issue additional ordinary shares.

The Company recorded \$0.5 million to research and development expense upon execution of the Oxford BioMedica Agreement in 2016 and \$0.1 million upon achievement of the first development milestone in 2017. The expense was determined based on the ordinary shares' fair value as of the time the agreement was executed.

The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

Other license and research agreements

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. As part of the consideration related to these license agreement, the total share commitment was 1,288,000 and 469,049 ordinary shares and the Company made cash payments of \$2.7 million and \$0.4 million in 2016 and 2017, respectively. The Company recorded \$3.2 million and \$1.7 million to research and development expense in 2016 and 2017, respectively. In addition, the Company also committed to make certain clinical and regulatory milestone payments in the aggregate of \$29.0 million as well as single-digit percentage royalties on net sales of products and services associated with the in-licensed technology.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

UCLA research agreement

In January 2017, the Company and UCLA executed a subcontract agreement (“UCLA Research Agreement”), whereby the Company would provide UCLA certain research and development services related to autologous lentiviral gene therapy in ADA-SCID as part of UCLA’s existing ADA-SCID research program that is being funded by the California Institute for Regenerative Medicine (“CIRM”). The total reimbursement the Company may receive under the UCLA Research Agreement is \$10.4 million, which may be received during the period from January 2017 to December 2021. The reimbursement is recognized as a reduction in research and development expense for research activities that have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM.

For the year ended December 31, 2017, the Company recorded \$5.0 million as a reduction of research and development expenses related to the UCLA Research Agreement. As of December 31, 2017, the Company recorded \$2.3 million within accrued expense and other liabilities on the Company’s consolidated balance sheet related to the advance of reimbursements for research activities.

9. Income taxes

The provision for income taxes for the years ended December 31, 2016 and 2017 was computed at the United Kingdom statutory income tax rate. The income tax provision for the years then ended comprised:

	December 31,	
	2016	2017
	(in thousands)	
Current provision expense		
Federal—United States	\$ —	\$ —
State—United States	17	16
United Kingdom	—	—
Total current provision expense	17	16
Deferred provision expense		
Federal—United States	—	—
State—United States	3	37
United Kingdom	—	—
Total deferred provision expense	3	37
Total provision for income taxes	\$ 20	\$ 53

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

A reconciliation of income tax expense computed at the United Kingdom statutory income tax rate to income taxes as reflected in the consolidated financial statements is as follows:

	December 31,	
	2016	2017
	(in thousands)	
Income taxes at United Kingdom statutory rate	\$(3,831)	\$(7,640)
State income taxes	14	41
Permanent differences	75	115
Tax credits	(99)	(286)
Foreign rate differential	6	(40)
Change in valuation allowance	3,855	7,827
Impact of United States tax reform	—	36
Total provision expense for income taxes	\$ 20	\$ 53

Significant components of the Company's deferred tax assets and liabilities as of December 31, 2016 and 2017 consist of the following:

	December 31,	
	2016	2017
	(in thousands)	
Deferred tax assets		
Net operating loss carryforwards	\$ 1,989	\$ 9,483
Research and development credits	70	356
Share-based compensation	15	147
Amortization	1,457	2,156
Accruals	14	28
Total deferred tax assets	3,545	12,170
Valuation allowance	(3,503)	(11,882)
Net deferred tax assets	\$ 42	\$ 288
Deferred tax liabilities		
Depreciation	\$ (44)	\$ (328)
Other non-current liabilities (net deferred tax assets and liabilities)	\$ (2)	\$ (40)

As of December 31, 2016, the Company has approximately \$9.9 million of United Kingdom net operating loss carryforwards with an indefinite life (but may be subject to certain utilization restrictions). Additionally, the Company has approximately \$0.1 million of United States federal research and development credit carryforwards that begin to expire in 2036.

As of December 31, 2017, the Company has approximately \$48.4 million of United Kingdom net operating loss carryforwards with an indefinite life (but may be subject to certain utilization restrictions). Additionally, the Company has approximately \$0.8 million and \$0.4 million of

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

United States federal net operating loss and federal research and development credit carryforwards that begin to expire in 2037 and 2036, respectively.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets, which primarily comprise net operating loss carryforwards and research and development credits. Management has considered the Company's history of cumulative net losses in the United States and United Kingdom, estimated future taxable income and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of its United States federal and United Kingdom deferred tax assets. Accordingly, a full valuation allowance has been established against these net deferred tax assets as of December 31, 2016 and 2017, respectively. The Company reevaluates the positive and negative evidence at each reporting period.

The Company files tax returns in the United Kingdom, United States and various U.S. states. With few exceptions, the Company is subject to United States federal, state and local, and foreign tax examinations by tax authorities from inception through present. As of December 31, 2017, the Company has recorded no liability for unrecognized tax benefits, interest, or penalties related to federal, state, and foreign income tax matters and there currently no pending tax examinations.

10. Net loss per share

The following table sets forth the computation of basic and diluted net loss per share:

	Year ended December 31	
	2016	2017
	(In thousands, except per share and share amounts)	
Net loss	\$ (19,085)	\$ (39,744)
Net loss attributable to ordinary shareholders	\$ (19,085)	\$ (39,744)
Weighted average ordinary shares outstanding, basic and diluted	8,872,333	11,086,808
Net loss per share attributable to ordinary shareholders, basic and diluted	\$ (2.15)	\$ (3.58)

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all shares convertible into ordinary shares outstanding would have been anti-dilutive.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following securities are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

	December 31,	
	2016	2017
Convertible preferred shares	14,000,000	41,581,513
Share options	2,260,966	4,513,663
	16,260,966	46,095,176

In 2018, the Company issued 625,511 ordinary shares to third-party licensors. In January 2018, the Company issued an additional 616,641 Series B convertible preferred shares. In April 2018, the Company issued 15,563,230 Series B-2 convertible preferred shares as consideration for the GSK Agreement (as defined in Note 14). In August 2018, the Company issued 17,421,600 Series C convertible preferred shares (Note 14).

Unaudited pro forma net loss per share attributable to ordinary shareholders

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. The following represents pro forma earnings per share information for Orchard Therapeutics plc for the years ended December 31, 2016 and 2017:

	Year ended December 31	
	2016	2017
	(in thousands except per share and share amounts)	
Net loss attributable to ordinary shareholders	\$ (19,085)	\$ (39,744)
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	\$ (2.69)	\$ (4.48)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	7,100,528	8,872,768

Unaudited supplemental pro forma net loss per share attributable to ordinary shareholders

The unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the year ended December 31, 2017 have been prepared to give effect to adjustments arising upon the closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2017 or the issuance date of the convertible preferred

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

A reconciliation of the pro forma weighted-average number of ordinary shares used in computing supplemental pro forma basic and diluted net loss per share applicable to ordinary shareholders is as follows:

	Year ended December 31, 2017
	(in thousands except per share and share amounts)
Numerator:	
Net loss attributable to ordinary shareholders	\$ (39,744)
Denominator	
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	8,872,768
Pro forma adjustment to reflect assumed conversion of preferred share into ordinary share (unaudited)	23,183,438
Supplemental pro forma weighted average number of ordinary shares used in computing supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	32,056,206
Supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	\$ (1.24)

11. Commitments and contingencies

Lease agreements

In October 2016, the Company entered into a lease agreement for five years for laboratory space in Foster City, California, United States. The lease commencement date was October 1, 2016. The Company was provided with one month of free rent.

In January 2017, the Company entered into a lease agreement for office space in London, United Kingdom. The lease commenced on January 16, 2017 and expires on January 16, 2019. 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.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

The following table summarizes the future minimum lease payments due under operating leases as of December 31, 2017:

Due in:	(in thousands)
2018	\$ 1,359
2019	1,029
2020	1,054
2021	191
Total	\$ 3,633

In January 2018, the Company leased office space in London, United Kingdom. The lease has a term of five years and terminates in January 2023. The annual rental commitment approximates \$0.8 million. In March 2018, the Company leased office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental commitment approximates \$0.3 million.

The Company recognizes rent expense on a straight-line basis over the respective lease period and has recorded deferred rent for rent expense incurred but not yet paid.

The Company recorded rent expense of \$0.2 million and \$0.7 million for the years ended December 31, 2016 and 2017, respectively.

License agreements

The Company has entered into several license agreements (Note 8). In connection with these agreements the Company is required to make a number of milestone payments and annual license maintenance payments. The Company evaluated all milestone payments within the arrangements to estimate the probability of the Company meeting the milestones. The Company concluded in November 2017 a milestone relating to Oxford BioMedica Agreement was met (Note 8), and as a result, the associated milestone consideration of \$0.1 million was recorded to research and development expense in the year ended December 31, 2017. The Company determined that no milestone payments were probable as of December 31, 2016.

Commitment with contract manufacturing organization

In 2017, Orchard entered into an agreement with a manufacturer of biotherapies in gene and cell therapies to purchase clinical material to be used in clinical trials. The Company has committed to place a minimum of three orders of clinical material over the next two years. The value of each order shall be determined by the specification and volume of the order placed. The Company expects to place two orders totaling \$2.1 million in 2018 and one order of \$1.1 million in 2019.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

12. Benefit plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to five percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid \$31,000 and \$0.2 million in matching contributions for the years ended December 31, 2016 and 2017, respectively.

13. Related-party transactions

UCLB

UCL Technology Fund LP ("UCLTF") is affiliated with UCLB. On February 6, 2016, UCLB through its associate UCLTF, entered into a Subscription and Shareholders' Agreement with the Company to purchase an aggregate of 999,999 Series A shares (Note 6). At the same time, UCLB also entered into the UCLB/UCLA License Agreement (Note 8), through which the Company was granted licenses to certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories. In 2016, the Company also agreed to sponsor a short-term research program with UCLB with total program costs of \$0.5 million. In 2016 and 2017, the Company incurred \$0.4 million and \$0.2 million of consulting fees, with an affiliate of UCLB, respectively.

Other

In December 2017, the Company sold to its Chief Executive Officer, Chief Medical Officer and Senior Vice President of Business Development and Alliance Management 49,763, 12,440 and 4,976 Series B convertible preferred shares at a price of £4.019 per share for proceeds of \$0.3 million, \$67,000 and \$27,000, respectively.

14. Subsequent events

For its consolidated financial statements as of December 31, 2017 and for the year then ended, the Company evaluated subsequent events through August 6, 2018, the date on which these financial statements were issued.

Additional ordinary shares issuance

In 2018, the Company issued 625,511 ordinary shares to third-party licensors as consideration for the in-licensing of technology relevant to its program in settlement of obligations accrued as of December 31, 2017.

Additional Series B issuance

In January 2018, the Company issued 616,641 Series B convertible preferred shares to investors at £4.019 per share for gross proceeds of \$3.3 million, of which \$1.0 million was received in December 2017 (Note 6).

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

GSK asset purchase and license agreement

In April 2018, the Company entered into an asset purchase and license agreement (the “GSK Agreement”) with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital (“Telethon-OSR”). This complements and enhances the Company’s current portfolio.

The portfolio of programs and options acquired consists of:

- Two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS;
- One earlier stage clinical gene therapy program for TDBT;
- Strimvelis, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for mucopolysaccharidosis type 1 (“MPS-I” or “Hurler syndrome”), chronic granulomatous disease (“CGD”), and globoid cell leukodystrophy (“GLD”).

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration of £94.2 million (\$133.6 million as of date of acquisition), which includes an upfront payment of £10.0 million (\$14.2 million at the acquisition date) and 15,563,230 Series B-2 convertible preferred shares of the Company issued to GSK at £65.8 million (\$93.4 million at the acquisition date), an inventory purchase liability valued at £4.9 million (\$6.9 million) and transaction costs of £0.6 million (\$0.8 million). The Company has allocated £94.2 million (\$133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development).

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million (\$92.4 million) representing the estimated fair value of the Priority Review Vouchers (“PRVs”), and associated liabilities in the amount of £41.9 million (\$59.4 million) representing the estimated fair value of the Company’s obligations under the GSK Agreement. The Company has since determined that the PRVs and associated liabilities did not meet the criteria for recognition due to their contingent nature based on their dependence of FDA approval of the underlying development program, and accordingly, has corrected this misstatement in the initial accounting for the GSK Agreement as of and for the six months ended June 30, 2018.

The Company is required to use commercially reasonable efforts to obtain a PRV from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDBT, the first of which GSK retained beneficial ownership. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDBT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

GSK. As described above, the Company has no longer reflected a liability related to the PRV because the contingent liability was not probable and could not be reasonably estimated at the time of the transaction.

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site.

Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability of £12.9 million (\$18.4 million at the acquisition date). This liability will be amortized on a straight-line basis over twenty five months which is the remaining period of expected sales of Strimvelis as a credit to research and development expenses. During the six months ended June 30, 2018, the Company amortized \$1.4 million as a credit to research and development expenses. The consideration transferred in the asset acquisition was measured at cost, including transaction costs, assets and equity interests transferred by the acquirer, and liabilities incurred by the acquirer as noted below:

	Consideration (as restated) (in thousands)
Upfront cash paid for GSK Agreement	\$ 14,186
Series B-2 convertible preferred shares issued to GSK	93,391
Transaction costs	780
Liabilities:	
Strimvelis liability	18,351
Inventory purchase liability	6,893
Total consideration transferred:	\$ 133,601

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

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

The Company and GSK have also separately executed a Transition Services Agreement ("TSA") as well as an Inventory Sale Agreement, both effective April 11, 2018. The TSA outlines several activities that the Company has requested GSK to assist with during the transition period, including but not limited to utilizing GSK to sell, market and distribute Strimvelis, and assist with regulatory, clinical and non-clinical activities for the other non-commercialized products which were ongoing at the date of the GSK Agreement. The TSA is scheduled to expire in December 2018.

In connection with the Company's entering into the GSK Agreement, GSK assigned rights and obligations to certain contracts, which include among others, the original license agreement with Telethon/Ospedale San Raffaele and an ongoing manufacturing agreement.

Telethon-OSR research and development collaboration and license agreement

In connection with the Company's entering into the GSK Agreement, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDBT, CGD, MPS-I and GLD.

As consideration for the licenses and options granted, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones and pay Telethon-OSR a fee in connection with the exercise of an option for each collaboration program. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement.

Series C issuance

In August 2018, the Company sold 17,421,600 Series C convertible preferred shares at a price of \$8.61 per share for gross proceeds of approximately \$150.0 million. The rights, preferences and privileges for the Series C convertible preferred shares are similar to those of the convertible preferred shares described in Note 6.

As part of the Series C financing, the Company sold to several of its executives and members of its board of directors Series C convertible preferred shares at a price of \$8.61 per share.

Events subsequent to original issuance of financial statements (unaudited)

In connection with the reissuance of the financial statements, the Company has evaluated subsequent events through October 23, 2018, the date the financial statements were reissued.

Orchard Therapeutics Limited

Notes to consolidated financial statements (continued)

Grants of stock options under the 2016 Plan

From January 1, 2018 to September 14, 2018, the Company granted options to employees and one of our new directors for the purchase of an aggregate of 3,085,388 ordinary shares, at a weighted average exercise price of \$4.97 per share. The aggregate grant-date fair value of these options was \$15.6 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

On September 25, 2018, the Company granted options to employees and consultants for the purchase of an aggregate of 242,500 ordinary shares, at a weighted average exercise price of \$3.62 per share. The aggregate grant-date fair value of these options was \$1.7 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

Orchard Therapeutics Limited

Unaudited condensed consolidated balance sheets

(In thousands, except share and per share amounts)

	December 31, 2017	June 30, 2018 (as restated)	Supplemental Pro forma June 30, 2018 (as restated)
Assets			
Current assets:			
Cash	\$ 89,856	\$ 48,762	\$ 48,762
Other receivables	1,247	428	428
Prepaid expenses and other current assets	3,118	8,863	8,863
Total current assets	94,221	58,053	58,053
Non-current assets:			
Property and equipment, net	2,713	5,342	5,342
Other long-term receivables	360	1,251	1,251
Total non-current assets	3,073	6,593	6,593
Total assets	\$ 97,294	\$ 64,646	\$ 64,646
Liabilities and shareholders' equity			
Current liabilities:			
Accounts payable	\$ 3,891	\$ 13,614	\$ 13,614
Accrued expenses and other current liabilities	6,864	28,669	28,669
Total current liabilities	10,755	42,283	42,283
Other long-term liabilities	134	7,617	7,617
Total liabilities	10,889	49,900	49,900
Commitments and contingencies (Note 11)			
Shareholders' equity:			
Convertible preferred shares, £0.00001 par value; 42,198,154 and 57,761,384 shares authorized as of December 31, 2017 and June 30, 2018, respectively; 41,581,513 and 57,761,384 shares issued and outstanding as of December 31, 2017 and June 30, 2018, respectively; nil shares issued and outstanding as of June 30, 2018 (supplemental pro forma)	134,069	229,709	—
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,413 of shares at December 31, 2017 and June 30, 2018, respectively; 11,154,720 and 11,793,356 shares issued and outstanding at December 31, 2017 and June 30, 2018, respectively; 69,554,740 shares issued and outstanding at June 30, 2018 (supplemental pro forma)	—	—	1
Additional paid-in capital	7,610	9,885	239,593
Accumulated other comprehensive income	4,127	6,097	6,097
Accumulated deficit	(59,401)	(230,945)	(230,945)
Total shareholders' equity	86,405	14,746	14,746
Total liabilities and shareholders' equity	\$ 97,294	\$ 64,646	\$ 64,646

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited

Unaudited condensed consolidated statements of operations and comprehensive loss

(In thousands, except share and per share amounts)

	Six months ended June 30,	
	2017	2018 (as restated)
Operating expenses:		
Research and development	\$ 10,546	\$ 160,162
General and administrative	2,270	11,948
Total operating expenses	12,816	172,110
Loss from operations	(12,816)	(172,110)
Other income (expense):		
Other (expense) income	(400)	401
Total other (expense) income, net	(400)	401
Net loss before income tax	(13,216)	(171,709)
Income tax benefit	42	165
Net loss attributable to ordinary shareholders	\$ (13,174)	\$ (171,544)
Other comprehensive income		
Foreign currency translation adjustment	2,070	1,970
Total comprehensive loss	\$ (11,104)	\$ (169,574)
Net loss per share attributable to ordinary shareholders, basic and diluted	\$ (1.24)	\$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	10,648,967	12,615,109
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted	\$ (1.55)	\$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted	8,522,366	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shareholders, basic and diluted		\$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basis and diluted		49,349,711

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited
Unaudited condensed consolidated statement of shareholders' equity
(In thousands, except share amounts)

	Convertible preferred shares		Ordinary shares		Additional paid-in capital	Accumulated other comprehensive income	Accumulated deficit	Total
	Shares	Amount	Shares	Amount				
Balance at December 31, 2017	41,581,513	\$134,069	11,154,720	\$ —	\$ 7,610	\$ 4,127	\$ (59,401)	\$86,405
Issuance of convertible preferred shares, net of issuance costs	16,179,871	95,640	—	—	—	—	—	95,640
Exercise of options.	—	—	13,125	—	25	—	—	25
Share-based compensation expense.	—	—	—	—	2,250	—	—	2,250
Ordinary shares issued as part of license agreements.	—	—	625,511	—	—	—	—	—
Foreign currency translation adjustment (as restated)	—	—	—	—	—	1,970	—	1,970
Net loss (as restated)	—	—	—	—	—	—	(171,544)	(171,544)
Balance at June 30, 2018 (as restated).	57,761,384	\$229,709	11,793,356	\$ —	\$ 9,885	\$ 6,097	\$ (230,945)	\$14,746

See accompanying notes to unaudited condensed consolidated financial statements

Orchard Therapeutics Limited

Unaudited condensed consolidated statements of cash flows

(In thousands, except share amounts)

	Six months ended June 30,	
	2017	2018 (as restated)
Cash flows from operating activities		
Net loss	\$ (13,174)	\$ (171,544)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation expense	168	504
Share-based compensation	328	2,250
Non-cash consideration for licenses	—	93,391
Changes in components of operating assets and liabilities:		
Other receivables	(7,166)	(122)
Prepaid and other assets	(1,020)	(6,029)
Accounts payable	1,299	9,868
Accrued expenses and other current liabilities	4,933	22,812
Other long-term liabilities	(2)	7,795
Net cash used in operating activities	(14,634)	(41,075)
Cash flows from investing activities		
Purchases of property and equipment	(663)	(2,833)
Net cash used in investing activities	(663)	(2,833)
Cash flows from financing activities		
Proceeds from the issuance of convertible preferred shares, net of issuance costs	44,609	2,250
Proceeds from issuance of ordinary shares	—	25
Net cash provided by financing activities	44,609	2,275
Effect of exchange rate changes on cash	2,102	539
Net increase (decrease) in cash	31,414	(41,094)
Cash—beginning of period	3,497	89,856
Cash—end of period	\$ 34,911	\$ 48,762
Supplemental disclosure of non-cash investing and financing activities		
Settlement of tranche obligations	\$ 1,402	\$ —
Property and equipment included in accrued expenses and accounts payable at period end	\$ 543	\$ 357
Convertible preferred shares issued for licenses	\$ —	\$ 93,391

See accompanying notes to unaudited condensed consolidated financial statements.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements

Six months ended June 30, 2017 and 2018

(amounts in thousands, except share and per share data)

1. Basis of presentation

Basis of presentation

The accompanying unaudited condensed consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("GAAP") and include the accounts of the Company and its wholly owned subsidiaries, Orchard Therapeutics North America and Orchard Therapeutics Netherlands B.V., after elimination of all intercompany accounts and transactions.

The unaudited condensed consolidated interim financial statements have been prepared on the same basis as the audited annual consolidated financial statements as of and for the year ended December 31, 2017, and, in the opinion of management, reflect all adjustments, consisting of normal recurring adjustments, necessary for the fair statement of the Company's financial position as of June 30, 2018, and the results of its operations and its cash flows for the six months ended June 30, 2017 and 2018.

The results for the six months ended June 30, 2018 are not necessarily indicative of the results to be expected for the year ending December 31, 2018, any other interim periods, or any future year or period. These interim financial statements should be read in conjunction with the audited financial statements as of and for the year ended December 31, 2017, and the notes thereto, which are included elsewhere in this Registration Statement.

Through June 30, 2018, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares. The Company has incurred recurring losses since its inception, including net losses of \$13.2 million and \$171.5 million for the periods ended June 30, 2017 and 2018, respectively. As of June 30, 2018, the Company had an accumulated deficit of \$230.9 million. The Company expects to continue to generate operating losses for the foreseeable future. The Company expected that its cash on hand as of June 30, 2018 of \$48.8 million, together with the \$148.0 million of net cash proceeds received from the Company's sale of Series C convertible preferred shares in August 2018 (Note 13) will be sufficient to fund its operations and capital expenditure requirements through at least 12 months from the issuance date of these unaudited condensed consolidated financial statements.

Restatement of previously reported financial statements

The Company has restated its unaudited condensed consolidated financial statements as of and for the six months ended June 30, 2018, resulting from the determination that certain assets and liabilities related to the GSK asset purchase and license agreement transaction did not meet the criteria for recognition due to their contingent nature based on their dependence on FDA approval of the underlying development program.

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million (\$92.4 million) representing the estimated fair value of the Priority Review Vouchers ("PRVs"), and associated liabilities in the amount of £41.9 million (\$59.4 million) representing the

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

estimated fair value of the Company's obligations under the GSK agreement. The Company has corrected the misstatement by recording a decrease to intangible assets of £65.1 million (\$86.0 million) and decrease to liabilities of £41.9 million (\$55.3 million), in each instance as of June 30, 2018, and recording an increase to research and development expenses of £23.2 million (\$32.9 million) for the period ended June 30, 2018.

As a result, the Company has restated its unaudited condensed consolidated balance sheet, the related unaudited condensed consolidated statement of operations and comprehensive loss, unaudited condensed consolidated statement of shareholders' equity, and unaudited condensed consolidated statement of cash flows as of and for the period ended June 30, 2018. The impact of these adjustments is detailed in the tables below.

Unaudited condensed consolidated balance sheet

	Previously Reported	Adjustment	As Restated	Supplemental pro forma As Restated
Assets				
Current assets				
Cash	\$ 48,762	\$ —	\$ 48,762	\$ 48,762
Other receivables	428	—	428	428
Prepaid expenses and other current assets	8,863	—	8,863	8,863
Total current assets	58,053	—	58,053	58,053
Non-current assets:				
Property and equipment, net	\$ 5,342	\$ —	\$ 5,342	\$ 5,342
Intangible assets	86,005	(86,005)	—	—
Other long -term receivables	1,251	—	1,251	1,251
Total non-current assets	92,598	(86,005)	6,593	6,593
Total assets	\$ 150,651	\$ (86,005)	\$ 64,646	\$ 64,646
Liabilities and shareholders' equity				
Current liabilities				
Accounts payable	\$ 13,614	\$ —	\$ 13,614	\$ 13,614
Accrued expense and other current liabilities	28,669	—	28,669	28,669
Total current liabilities	42,283	—	42,283	42,283
Long-term liabilities				
Other long-term liabilities	62,950	(55,333)	7,617	7,617
Total long-term liabilities	62,950	(55,333)	7,617	7,617
Total liabilities	105,233	(55,333)	49,900	49,900

Commitments and contingencies (Note 11)

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

	Previously Reported	Adjustment	As Restated	Supplemental pro forma As Restated
Shareholders' equity				
Convertible preferred shares, £0.00001 par value; 42,198,154 and 57,761,384 shares authorized as of December 31, 2017 and June 30, 2018, respectively; 41,581,513 and 57,761,384 shares issued and outstanding as of December 31, 2017 and June 30, 2018, respectively; nil shares issued and outstanding as of June 30, 2018 (pro forma)	229,709	—	229,709	—
Ordinary shares, £0.00001 par value, authority to allot up to a maximum nominal value of £675,413 of shares at December 31, 2017 and June 30, 2018, respectively; 11,154,720 and 11,793,356 shares issued and outstanding at December 31, 2017 and June 30, 2018, respectively; 69,554,740 shares issued and outstanding at June 30, 2018 (pro forma)	—	—	—	1
Additional paid-in capital	9,885	—	9,885	239,593
Accumulated other comprehensive income	3,828	2,269	6,097	6,097
Accumulated deficit	(198,004)	(32,941)	(230,945)	(230,945)
Total shareholders' equity	45,418	(30,672)	14,746	14,746
Total liabilities and shareholders' equity	\$ 150,651	\$ (86,005)	\$ 64,646	\$ 64,646

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited condensed consolidated statement of operations and comprehensive loss

	Previously Reported	Adjustment	As Restated
Operating expenses:			
Research and development	\$ 127,221	\$ 32,941	\$ 160,162
General and administrative	11,948	—	11,948
Total operating expense	139,169	32,941	172,110
Loss from operations	(139,169)	(32,941)	(172,110)
Other income:			
Other income	401	—	401
Total other income	401	—	401
Net loss before income tax	(138,768)	(32,941)	(171,709)
Income tax benefit	165	—	165
Net loss attributable to ordinary shareholders	\$ (138,603)	\$ (32,941)	\$ (171,544)
Other comprehensive income			
Foreign currency translation adjustment	\$ (299)	\$ 2,269	\$ 1,970
Total comprehensive loss	\$ (138,902)	\$ (30,672)	\$ (169,574)
Net Loss per share attributable to ordinary shareholders, basic and diluted	\$ (10.99)	\$ (2.61)	\$ (13.60)
Weighted average number of ordinary shares outstanding, basic and diluted	12,615,109	—	12,615,109
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted	\$ (13.73)	\$ (3.26)	\$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted	10,095,863	—	10,095,863
Supplemental pro forma net loss per share attributable to ordinary shareholders, basic and diluted	\$ (2.81)	\$ (0.67)	\$ (3.48)
Supplemental pro forma weighted average number of ordinary shares outstanding, basic and diluted	49,349,711	—	49,349,711

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited condensed consolidated statements of cash flows

	Previously Reported	Adjustment	As Restated
Cash flows from operating activities			
Net loss	\$ (138,603)	\$ (32,941)	\$ (171,544)
Adjustments to reconcile net loss to net cash used in operating activities			
Depreciation expense	504	—	504
Share-based compensation	2,250	—	2,250
Non-cash consideration for licenses	61,229	32,162	93,391
Changes in components of operating assets and liabilities:			
Other receivables	(122)	—	(122)
Prepays and other assets	(6,029)	—	(6,029)
Accounts payable	9,111	757	9,868
Accrued expenses and other current liabilities	22,812	—	22,812
Other long-term liabilities	7,795	—	7,795
Net cash used in operating activities	<u>(41,053)</u>	<u>(22)</u>	<u>(41,075)</u>
Cash flows from investing activities			
Purchases of property and equipment	<u>(2,833)</u>	<u>—</u>	<u>(2,833)</u>
Net cash used in investing activities	<u>(2,833)</u>	<u>—</u>	<u>(2,833)</u>
Cash Flows from financing activities			
Proceeds from issuance of preferred shares, net of issuance costs	2,250	—	2,250
Proceeds from issuance of common stock	25	—	25
Net cash provided financing activities	<u>2,275</u>	<u>—</u>	<u>2,275</u>
Effect of exchange rate changes on cash and cash equivalents	517	22	539
Net decrease in cash	<u>(41,094)</u>	<u>—</u>	<u>(41,094)</u>
Cash-beginning of period	89,856	—	89,856
Cash-end of period	<u>\$ 48,762</u>	<u>\$ —</u>	<u>\$ 48,762</u>
Supplemental Disclosure of Non-Cash Investing and Financing Activities			
Property and equipment included in accrued expenses and accounts payable at period end	\$ 357	\$ —	\$ 357
Intangible assets included in accounts payable and other long-term liabilities	\$ 56,059	\$ (56,059)	\$ —
Convertible preferred shares issued for intangible assets	\$ 32,161	\$ (32,161)	\$ —
Convertible preferred shares issued for licenses	\$ 61,229	\$ 32,162	\$ 93,391

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

2. Summary of significant accounting policies

The Company's significant accounting policies are disclosed in the audited consolidated financial statements for the year ended December 31, 2017 included in the Company's audited financial statements included within their Form F-1. Since the date of such consolidated financial statements, there have been no changes to the Company's significant accounting policies.

Unaudited pro forma information

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. In the accompanying consolidated statements of operations and comprehensive loss, the unaudited pro forma information represents information for Orchard Therapeutics plc for the six months ended June 30, 2017 and 2018 (as restated).

Unaudited supplemental pro forma information

In the accompanying consolidated statements of operations and comprehensive loss, the unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the six months ended June 30, 2018 has been prepared to give effect to, upon closing of a qualified IPO (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

3. Prepaid expenses and other current assets

Prepaid expenses and other current assets consisted of the following:

	December 31, 2017	June 30, 2018
		(in thousands)
Prepaid external research and development costs	\$ 763	\$ 3,173
VAT receivable	1,042	832
RDEC receivable	871	4,085
Prepaid rent	259	252
Prepaid other	183	521
Total prepaid expenses and other current assets	\$ 3,118	\$ 8,863

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

4. Property and equipment

Property and equipment consist of the following:

	December 31, 2017	June 30, 2018
	(in thousands)	
Property and equipment		
Lab equipment	\$ 2,708	\$ 4,253
Leasehold improvements	244	1,447
Furniture and fixtures	59	340
Office and IT equipment	12	110
Property and equipment.	\$ 3,023	\$ 6,150
Less: accumulated depreciation.	(310)	(808)
Property and equipment, net.	\$ 2,713	\$ 5,342

Depreciation expense in the six months ended June 30, 2017 and 2018 was \$0.2 million and \$0.5 million, respectively.

5. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31, 2017	June 30, 2018
	(in thousands)	
Accrued external research and development expenses	\$ 1,834	\$ 15,361
Accrued payroll and related expenses	2,090	2,649
Accrued professional fees	394	1,934
Strimvelis liability—current portion	—	8,202
Accrued other	279	523
Deferred UCLA reimbursement	2,267	—
Total accrued expenses and other current liabilities	\$ 6,864	\$ 28,669

Included within accrued external research and development expenses as of June 30, 2018 was a payable of \$6.4 million to GSK relating to the GSK asset purchase and license agreement.

6. Shareholders' equity and convertible preferred shares

Convertible preferred shares

As of June 30, 2018, the Company's Articles of Association (the "Articles"), as further amended and restated (the "2018 Amended Articles"), authorized a total of 57,761,384 convertible preferred shares with a par value of £0.00001 per share, of which 21,000,000 shares have been designated as Series A convertible preferred shares, 21,198,154 shares have been designated as Series B convertible preferred shares and 15,563,230 shares have been designated as Series B-2

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

convertible preferred shares (the "Series B-2 convertible preferred shares"). The Series A, Series B and Series B-2 convertible preferred shares will be collectively referred to as the Convertible Preferred Shares.

Preferred share financings

In January 2018, the Company issued 616,641 Series B convertible preferred shares to investors at £4.019 per share for gross proceeds of \$3.3 million, of which \$1.0 million was received in December 2017.

In April 2018, the Company issued 15,563,230 Series B-2 convertible preferred shares to GSK pursuant to the Company entering into an asset purchase and license agreement (the "GSK Agreement") of which the Company valued the Series B-2 convertible preferred shares issued at \$93.4 million (Note 8).

As of each balance sheet, the Convertible Preferred Shares consisted of the following:

	December 31, 2017				
	(in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	\$ 26,994	\$ 28,337	21,000,000
Series B convertible preferred shares	21,198,154	20,581,513	107,075	111,617	20,581,513
	42,198,154	41,581,513	\$134,069	\$ 139,954	41,581,513

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2017.

	June 30, 2018				
	(in thousands, except share amounts)				
	Shares authorized	Shares issued and outstanding	Carrying value	Liquidation preference(a)	Ordinary shares issuable upon conversion
Series A convertible preferred shares	21,000,000	21,000,000	\$ 26,994	\$ 27,739	21,000,000
Series B convertible preferred shares	21,198,154	21,198,154	109,324	112,534	21,198,154
Series B-2 convertible preferred shares	15,563,230	15,563,230	93,391	82,620	15,563,230
	57,761,384	57,761,384	\$229,709	\$ 222,893	57,761,384

(a) Amounts were translated into United States dollars using the spot rate as of June 30, 2018.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The holders of the Convertible Preferred Shares as of June 30, 2018 have the same rights and preference disclosed in the Company's annual financial statements with the exception of certain voting rights related to Series B-2 convertible preferred shares as described below:

Voting

Each Series A and Series B share shall confer one right to vote at all general meetings and to receive and vote on proposed written resolutions of the Company. In respect of the Series B-2 convertible preferred shares only fifty percent of the total number of Series B-2 convertible preferred shares held by GSK shall be treated as having voting rights and all remaining Series B-2 convertible preferred shares in issue shall be disregarded for purposes of voting at any general meeting of the Company or for the purposes of any proposed written resolutions.

Ordinary shares

Ordinary share issuances

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. In 2018, the Company issued 437,049 ordinary shares to third-party licensors as consideration for the in-licensing of technology relevant to its program in settlement of obligations accrued as of December 31, 2017.

In June 2018, the Company issued 188,462 ordinary shares to Oxford BioMedica for a milestone that was achieved in November 2017.

As of December 31, 2017 and June 30, 2018, the Company had outstanding 11,154,720 and 11,793,356 ordinary shares, respectively.

7. Share-based compensation

2016 Share option plan

In September 2016, the Company adopted the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"). The 2016 Plan provides for the Company to grant incentive and non-qualified options to officers, directors, consultants, and advisors to purchase the Company's ordinary shares.

The total number of ordinary shares that may be issued under the 2016 Plan was 11,800,000 shares as of June 30, 2018 of which 2,433,172 shares remained available for future grant.

During the six months ended June 30, 2017 and 2018, the Company granted options to purchase 528,100 and 4,384,781 shares of ordinary shares, respectively, to employees, nonemployees and directors. The Company recorded share-based compensation expense for options granted to employees, nonemployees and directors of \$0.3 million and \$2.2 million during the six months ended June 30, 2017 and 2018, respectively.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Option valuation

When utilizing the Black-Scholes option-pricing model to determine the grant date fair value of share options granted in the six months ended June 30, 2017 and 2018, the Company used the following assumptions:

Employee, Nonemployees and directors

	Six months ended June 30,	
	2017	2018
Risk-free interest rate	2.13%	2.66% - 2.83%
Expected term (in years)	6.08	6.08
Expected volatility	80.00%	66.51% - 68.17%
Expected dividend rate	0.00%	0.00%

Options

The following table summarizes option activity under the 2016 Plan since December 31, 2017:

	Shares	Weighted average exercise price	Weighted average remaining contractual life	Aggregate intrinsic value
(in thousands, except share and per share amounts)				
Options outstanding at December 31, 2017	5,223,443	\$ 0.96	9.28	\$ 10,483
Granted	4,382,511	1.67		
Exercised	(13,125)	1.95		
Cancelled	(226,001)	0.49		
Options outstanding at June 30, 2018	9,366,828	\$ 1.30	9.21	\$ 36,803
Vested as of June 30, 2018	1,394,330	\$ 0.22	8.33	\$ 6,964

The weighted average exercise price of options granted to United Kingdom employees in the six months ended June 30, 2018 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees in the six months ended June 30, 2018 was \$2.51.

The aggregate intrinsic value of options is calculated as the difference between the exercise price of the options and the fair value of the Company's ordinary shares for those options that had exercise prices lower than the fair value of the Company's ordinary shares.

The weighted average grant date fair value of the options granted during the six months ended June 30, 2017 and 2018, was \$1.63 per share and \$3.34 per share, respectively.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Share-based compensation

Share-based compensation expense was classified in the consolidated statements of operations and comprehensive loss as follows:

	Six months ended June 30,	
	2017	2018
	(in thousands)	
Research and development	\$ 247	\$ 674
General and administrative	81	1,576
Total	\$ 328	\$ 2,250

The Company had 7,974,768 unvested options outstanding as of June 30, 2018. As of June 30, 2018, there was \$17.1 million of unrecognized compensation expense related to unvested options, that is expected to be recognized over a weighted average period of approximately 3.25 years.

8. License and research arrangements

GSK asset purchase and license agreement

In April 2018, the Company entered into an asset purchase and license agreement (the "GSK Agreement") with subsidiaries of GSK to acquire a portfolio of autologous *ex vivo* gene therapy assets and licenses, for rare diseases and option rights on three additional programs in preclinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). This complements and enhances the Company's current portfolio.

The portfolio of programs and options acquired consists of:

- Two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS;
- One earlier stage clinical gene therapy program for TDBT;
- Strimvelis, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for mucopolysaccharidosis type 1 ("MPS-I" or "Hurler syndrome"), chronic granulomatous disease ("CGD"), and globoid cell leukodystrophy ("GLD").

The Company accounted for the GSK Agreement as an asset acquisition, since the asset purchase and licensing arrangement did not meet the definition of a business pursuant to ASC 805, Business Combinations. Total consideration of £94.2 million (\$133.6 million as of date of acquisition), which includes an upfront payment of £10.0 million (\$14.2 million at the acquisition date) and 15,563,230 Series B-2 convertible preferred shares of the Company issued to GSK valued at £65.8 million (\$93.4 million at the acquisition date), an inventory purchase liability

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

valued at £4.9 million (\$6.9 million) and transaction costs of £0.6 million (\$0.8 million). The Company has allocated £94.2 million (\$133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development).

The Company had previously recorded indefinite lived intangible assets in the amount of £65.1 million (\$92.4 million) representing the estimated fair value of the Priority Review Vouchers ("PRVs"), and associated liabilities in the amount of £41.9 million (\$59.4 million) representing the estimated fair value of the Company's obligations under the GSK Agreement. The Company has since determined that the PRVs and associated liabilities did not meet the criteria for recognition due to their contingent nature based on their dependence of FDA approval of the underlying development program, and accordingly, has corrected this misstatement in the initial accounting for the GSK Agreement as of and for the six months ended June 30, 2018.

The Company is required to use commercially reasonable efforts to obtain a PRV from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDBT and to, the first of which GSK retained beneficial ownership. GSK also has an option to acquire, at a price pursuant to an agreed upon formula, any PRV granted to the Company thereafter for MLD, WAS and TDBT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As described above, the Company has no longer reflected a liability related to the PRV because the contingent liability was not probable and could not be reasonably estimated at the time of the transaction.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy, such as our OTL-101 product candidate, is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site.

Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability of £12.9 million (\$18.4 million at the acquisition date). This liability will be amortized on a straight-line basis over twenty five months which is the remaining period of expected sales of Strimvelis as a credit to research and development expenses. During the six months ended June 30, 2018, the Company amortized \$1.4 million as a credit to research and development expenses. The consideration transferred in the asset acquisition was measured at cost, including transaction costs, assets and equity interests transferred by the acquirer, and liabilities incurred by the acquirer as noted below:

	Consideration (as restated)
	(in thousands)
Upfront cash paid for GSK Agreement	\$ 14,186
Series B-2 convertible preferred shares issued to GSK	93,391
Transaction costs	780
Liabilities:	
Strimvelis liability	18,351
Inventory purchase liability	6,893
Total consideration transferred:	\$ 133,601

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired and OTL-101. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes Strimvelis and the Company-developed product candidate, OTL-101. The Company will also pay tiered royalty rates at percentage beginning in the mid-teens up to twenty percent for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. The Company will pay a tiered royalty at percentage from the high single-digits to low double-digit for the TDBT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDBT product. These royalties owed to GSK are in addition to any royalties owed to other third parties under various license agreements for the GSK programs. In aggregate, the Company may pay up to £90.0 million of milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars, and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The Company and GSK have also separately executed a Transition Services Agreement (“TSA”) as well as an Inventory Sale Agreement, both effective April 11, 2018. The TSA outlines several activities that the Company has requested GSK to assist with during the transition period, including but not limited to utilizing GSK to sell, market and distribute Strimvelis, and assist with regulatory, clinical and non-clinical activities for the other non-commercialized products which were ongoing at the date of the GSK Agreement. The TSA is scheduled to expire in December 2018.

In connection with the Company’s entering into the GSK Agreement, GSK assigned rights and obligations to certain contracts, which include among others, the original license agreement with Telethon/Ospedale San Raffaele and an ongoing manufacturing agreement.

Telethon-OSR research and development collaboration and license agreement

In connection with the Company’s entering into the GSK Agreement, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDBT, CGD, MPS-I and GLD.

The Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones and pay Telethon-OSR a fee in connection with the exercise of an option for each collaboration program. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement. In aggregate, the Company may pay up to \$120.3 million of milestone payments upon achievement of certain product development milestones and exercises of options under the Telethon-OSR agreements.

UCLB/UCLA License Agreement

In February 2016, and amended in July 2017, the Company entered into the UCLB/UCLA License Agreement, under which the Company has been granted exclusive and non-exclusive, sublicensable licenses under certain intellectual property rights controlled by UCLB and UCLA to develop and commercialize gene therapy products in certain fields and territories.

In exchange for these rights, in 2016, the Company made upfront cash payments consisting of \$0.8 million for the license to the joint UCLB/UCLA technology and \$1.1 million for the license to the UCLB technology and manufacturing technology. The Company also issued an aggregate of 5,829,545 ordinary shares to UCLB, of which 4,300,000 and 1,529,545 ordinary shares were issued in 2016 and 2017, respectively. The Company recorded research and development expense based on the fair value of the ordinary shares as of the time the agreement was executed. The Company was also obligated to make an additional cash payment for clinical data. In 2017, the Company paid \$0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of \$0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company is obligated to make payments to the parties of up to an aggregate of \$38.9 million upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

The Company recorded \$0.1 million for research and development costs in the six months ended June 30, 2017 and 2018.

Unless terminated earlier by either party, the UCLB/UCLA License Agreement will expire on the 25th anniversary of the agreement.

Oxford BioMedica license, development and supply agreement

In November 2016, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors for the Company ("Oxford BioMedica Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 735,000 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved and the Company was committed to issue 188,462 ordinary shares in 2018. As of June 30, 2018, the Company's remaining potential share obligation under the agreement comprised one milestone, which, upon achievement, would require the Company to issue additional ordinary shares.

The Company recorded \$0.5 million to research and development expense upon execution of the Oxford BioMedica Agreement in 2016 and \$0.1 million upon achievement of the first development milestone in 2017. The expense was determined based on the ordinary shares' fair value as of the time the agreement was executed. There were no amounts recorded to research and development expense in the six months ended June 30, 2017 and 2018 related to the Oxford BioMedica Agreement.

The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

Other license and research agreements

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. As part of the consideration related to these license agreements, the total share commitment was 1,288,000 and 469,049 ordinary shares and the Company made cash payments of \$2.7 million and \$0.4 million in 2016 and 2017, respectively. The Company recorded nil and \$0.6 million to research and development expense in the six months ended June 30, 2017

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

and 2018, respectively. In addition, the Company also committed to make certain clinical and regulatory milestone payments in the aggregate of \$31.8 million as well as single-digit percent royalties on net sales of products and services associated with in-licensed technology.

UCLA research agreement

In January 2017, the Company and UCLA executed a subcontract agreement (“UCLA Research Agreement”), whereby the Company would provide UCLA certain research and development services related to autologous lentiviral gene therapy in ADA-SCID as part of UCLA’s existing ADA-SCID research program that is being funded by the California Institute for Regenerative Medicine (“CIRM”). The total reimbursement the Company may receive under the UCLA Research Agreement is \$10.4 million, which may be received during the period from January 2017 to December 2021. The reimbursement is recognized as a reduction in research and development expense for research activities that have taken place. In the event the reimbursement is received in advance of research activities, it is recognized within other liabilities. In the event the Company has performed reimbursable research activities and has not been reimbursed, it is recognized within prepaid expenses and other current assets. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM.

In the six months ended June 30, 2017 and 2018, the Company recorded \$3.7 million and \$2.4 million as a reduction of research and development expenses related to the UCLA Research Agreement. As of June 30, 2018, the Company recorded \$0.2 million within prepaid expenses and other current assets on the Company’s condensed consolidated balance sheet related to research activities performed that have not reimbursed.

9. Income Taxes

The benefit for income taxes for the six months ended June 30, 2017 and 2018 was \$42,000 and \$165,000, respectively. The tax benefit for the six months ended June 30, 2018 consisted primarily of the reversal of a deferred tax liability in the United States.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize its deferred tax assets, which are comprised primarily of net operating loss carryforwards and research and development credits. Management has considered the Company’s history of cumulative net losses in the United States and United Kingdom, estimated future taxable income and prudent and feasible tax planning strategies and has concluded that it is more likely than not that the Company will not realize the benefits of its United States and United Kingdom deferred tax assets. Accordingly, the Company maintains a full valuation allowance against these net deferred tax assets as of June 30, 2018.

The Company files tax returns in the United States, various states, and foreign jurisdictions. With few exceptions, the Company is subject to U.S. federal, state and local, and foreign tax examinations by tax authorities for years 2016 through present. As of June 30, 2018, the Company has not recorded a liability for unrecognized tax benefits, interest, or penalties related to federal, state, and foreign income tax matters and there currently no pending tax examinations.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

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

As a company that carries out extensive research and development activities, the Company seeks to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises Research and Development Tax Credit Program ("SME Program") and the Research and Development Expenditure program ("RDEC Program"). Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income. Such credits are accounted as reductions in research and development expense in the period in which the expenditures were incurred.

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

The Company has recorded United Kingdom research and development tax credit as an offset to research and development expense in the consolidated statements of operations and comprehensive loss of \$0.2 million and \$3.6 million for the periods ended June 30, 2017 and 2018, respectively. As of June 30, 2018, the Company's tax incentive receivable from the United Kingdom government was \$4.1 million. These amounts have not yet been paid to the Company by HMRC.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

10. Net loss per share

The following table sets forth the computation of basic and diluted net loss per share:

	Six months ended June 30,	
	2017	2018 (as restated)
	(In thousands, except per share and share amounts)	
Net loss	\$ (13,174)	\$ (171,544)
Net loss attributable to ordinary shareholders	\$ (13,174)	\$ (171,544)
Weighted average ordinary shares outstanding, basic and diluted	10,648,967	12,615,109
Net loss per share attributable to ordinary shareholders, basic and diluted	\$ (1.24)	\$ (13.60)

Since the Company was in a loss position for all periods presented, basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all shares convertible into ordinary shares outstanding would have been anti-dilutive.

The following securities are considered to be ordinary share equivalents, but were not included in the computation of diluted net loss per ordinary share because to do so would have been anti-dilutive:

	Six Months Ended June 30,	
	2017	2018
Convertible preferred shares	28,254,000	57,761,384
Share options	2,408,482	9,070,186
	30,662,482	66,831,570

In August 2018, the Company issued 17,421,600 Series C convertible preferred shares (Note 13).

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Unaudited pro forma net loss per share attributable to ordinary shareholders

Orchard Rx Limited was incorporated in August 2018 to become the holding company of Orchard Therapeutics Limited. Prior to the IPO of Orchard Rx Limited, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited, and Orchard Rx Limited will re-register as a public company and change its name to Orchard Therapeutics plc. Orchard Therapeutics plc's financial statements will be the same as Orchard Therapeutics Limited's financial statements prior to the IPO after adjusting retrospectively for the Orchard Therapeutics plc capital structure, which includes a 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO. The following represents pro forma earnings per share information for Orchard Therapeutics plc for the six months ended June 30, 2017 and 2018 (as restated):

	Six months ended June 30,	
	2017	2018
	(as restated)	
	(in thousands except per share and share amounts)	
Net loss attributable to ordinary shareholders	\$ (13,174)	\$ (171,544)
Pro forma net loss per share attributable to ordinary shareholders, basic and diluted (unaudited)	\$ (1.55)	\$ (16.99)
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	8,522,366	10,095,863

Unaudited supplemental pro forma net loss per share attributable to ordinary shareholders

The unaudited supplemental pro forma basic and diluted net loss per share attributable to ordinary shareholders for the six months ended June 30, 2018 (as restated) have been prepared to give effect to adjustments arising upon the closing of a qualified IPO, (i) the automatic conversion of all outstanding shares of the convertible preferred shares into ordinary shares as if the conversion had occurred on the later of January 1, 2018 or the issuance date of the convertible preferred shares, and (ii) the 1-for-0.8003 reverse split of our ordinary and preferred shares to be effected immediately prior to the completion of the IPO.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

A reconciliation of the pro forma weighted-average number of ordinary shares used in computing supplemental pro forma basic and diluted net loss per share applicable to ordinary shareholders is as follows:

	Six months ended June 30, 2018 (as restated)
	(in thousands except per share and share amounts)
Numerator:	
Net loss attributable to ordinary shareholders	\$ (171,544)
Denominator	
Pro forma weighted average number of ordinary shares outstanding, basic and diluted (unaudited)	10,095,863
Pro forma adjustment to reflect assumed conversion of preferred share into ordinary share (unaudited)	<u>39,253,848</u>
Supplemental pro forma weighted average number of ordinary shares used in computing supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	<u>49,349,711</u>
Supplemental pro forma net loss per share attributable to ordinary shareholders – basic and diluted (unaudited)	\$ (3.48)

11. Commitments and contingencies

Lease agreements

In October 2016, the Company entered into a lease agreement for five years for laboratory space in Foster City, California, United States. The lease commencement date was October 1, 2016. The Company was provided with one month of free rent.

In January 2017, the Company entered into a lease agreement for office space in London, United Kingdom. The lease commenced on January 16, 2017 and expires on January 16, 2019. Management has the option to terminate the lease at its discretion after at the end of the one year anniversary of the lease.

In November 2017, the Company entered into a lease arrangement for laboratory space in Menlo Park, California, United States. The lease commenced on November 1, 2017 and expires on November 30, 2020. The Company was provided with one month of free rent.

In January 2018, the Company leased office space in London, United Kingdom. The lease has a term of five years and terminates in January 2023. The annual rental commitment approximates \$0.8 million.

In March 2018, the Company leased office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental commitment approximates \$0.3 million.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

The Company recognizes rent expense on a straight-line basis over the respective lease period and has recorded deferred rent for rent expense incurred but not yet paid.

The Company recorded rent expense of \$0.3 million and \$1.2 million in the six months ended June 30, 2017 and 2018, respectively.

License agreements

The Company has entered into several license agreements (Note 8). In connection with these agreements the Company is required to make a number of milestone payments and annual license maintenance payments. The Company evaluated all milestone payments within the arrangements to estimate the probability of the Company meeting the milestones. The Company concluded in November 2017 a milestone relating to the Oxford BioMedica Agreement was met (Note 8), and as a result, the associated milestone consideration of \$0.1 million was recorded to research and development expense in the year ended December 31, 2017. The Company determined that no milestone payments were probable as of June 30, 2018.

Commitment with contract manufacturing organization

The Company has entered into agreements with contract manufacturing organizations relating to the provision of manufacturing services and purchase of clinical material to be used in clinical trials that include minimum purchase commitments. As of June 30, 2018, \$1.1m (2017: nil) included within prepayments relates to prepaid instalments against these minimum commitments. The Company is committed to make further payments totaling \$9.2 million between September 2018 and March 2020.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

12. Benefit plans

The Company makes contributions to private defined contribution pension plans on behalf of its employees. The Company matches its employee contributions up to five percent of each employee's annual salary based on the jurisdiction the employees are located. The Company paid \$0.1 million and \$ 0.2 million in matching contributions in the six months ended June 30, 2017 and 2018, respectively.

13. Subsequent events

The Company evaluated subsequent events through September 14, 2018, the date on which these financial statements were issued.

Orchard Therapeutics Limited

Notes to unaudited condensed consolidated financial statements (continued)

Telethon-OSR research and development collaboration and license agreement

In July 2018, the first patient was enrolled and dosed in the MPS-1 clinical study which in accordance with the license agreement triggered a milestone payment of \$1.8 million payable by the Company.

Series C issuance

In August 2018, the Company sold 17,421,600 Series C convertible preferred shares at a price of \$8.61 per share for net proceeds of approximately \$148.0 million. The rights, preferences and privileges for the Series C convertible preferred shares are similar to those of the convertible preferred shares described in Note 6.

As part of the Series C financing, the Company sold 406,504 shares of Series C convertible preferred shares at a price of \$8.61 per share to several of its executives and members of its board of directors for proceeds of \$3.5 million.

Grants of stock options under the 2016 Plan

From July 1, 2018 to September 14, 2018, the Company granted options to employees and one of our new directors for the purchase of an aggregate of 3,085,388 ordinary shares, at a weighted average exercise price of \$4.97 per share. The aggregate grant-date fair value of these options was \$15.6 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

On September 25, 2018, the Company granted options to employees and consultants for the purchase of an aggregate of 242,500 ordinary shares, at a weighted average exercise price of \$3.62 per share. The aggregate grant-date fair value of these options was \$1.7 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years.

Events subsequent to original issuance of financial statements

In connection with the reissuance of the financial statements, the Company has evaluated subsequent events through October 23, 2018, the date the financial statements were reissued.

***14,285,715 American Depositary Shares
Representing 14,285,715 Ordinary Shares***



PROSPECTUS

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

October 30, 2018

Through and including November 24, 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.