UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 20-F

(Mark One)

☐ **REGISTRATION STATEMENT PURSUANT TO SECTION 12(b) OR (g) OF THE SECURITIES EXCHANGE ACT OF 1934**

OR

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2018

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

for the transition period from _____ to _____.

OR

☐ **SHELL COMPANY REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission file number: 001-38722

ORCHARD THERAPEUTICS PLC

(Exact name of Registrant as specified in its charter)

England and Wales
(Jurisdiction of incorporation)

108 Cannon Street
London EC4N 6EU
United Kingdom
(Address of principal executive offices)

Mark Rothera, President and Chief Executive Officer
Orchard Therapeutics plc
108 Cannon Street
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(Name, Telephone, E-mail and/or Facsimile number and Address of Company Contact Person)

Securities registered or to be registered, pursuant to Section 12(b) of the Act

Title of each class	Name of each exchange on which registered
American Depositary Shares, each representing one ordinary share, nominal value of £0.10 per share	The Nasdaq Stock Market LLC
Ordinary shares, nominal value £0.10 per share*	The Nasdaq Stock Market LLC*

*Not for trading, but only in connection with registration of American Depositary Shares.

Securities registered or to be registered pursuant to Section 12(g) of the Act: None

Securities for which there is a reporting obligation pursuant to Section 15(d) of the Act: None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

If this report is an annual or transition report, indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934. Yes ☐ No ☒

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer ☐ Accelerated filer ☐ Non-accelerated filer ☒ Emerging growth company ☒

If an emerging growth company that prepares its financial statements in accordance with U.S. GAAP, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards † provided pursuant to Section 13(a) of the Exchange Act. ☐

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

Indicate by check mark which basis of accounting the registrant has used to prepare the financial statements included in this filing:

U.S. GAAP ☒International Financial Reporting Standards as issued by the International Accounting Standards Board ☐Other ☐

If "Other" has been checked in response to the previous question indicate by check mark which financial statement item the registrant has elected to follow. Item 17 ☐ Item 18 ☐

If this is an annual report, indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

Indicate the number of outstanding shares of each of the issuer's classes of capital stock or common stock as of the close of business covered by the annual report. 85,865,557 ordinary shares, nominal value £0.10 per share, as of December 31, 2018

TABLE OF CONTENTS

PRESENTATION OF FINANCIAL AND OTHER INFORMATION

The consolidated financial statement data at December 31, 2018 and 2017 and for the years ended December 31, 2018, 2017, and 2016 have been derived from our consolidated financial statements, as presented elsewhere in this Annual Report, which have been prepared in accordance with generally accepted accounting principles in the United States, or U.S. GAAP, as issued by the Financial Accounting Standards Board, or FASB. The consolidated financial statement data at December 31, 2016 have been derived from our consolidated financial statements, which are not presented herein, which have also been prepared in accordance with U.S. GAAP as issued by the FASB.

All references in this Annual Report to "$" are to U.S. dollars and all references to "£" are to pounds sterling. Solely for the convenience of the reader, unless otherwise indicated, all pounds sterling amounts as of and for the year ended December 31, 2018 have been translated into U.S. dollars at the rate of £1.2687 to $1.00, which was the noon buying rate of the Federal Reserve Bank of New York on December 31, 2018, the last business day of the fiscal year ended December 31, 2018. These translations should not be considered representations that any such amounts have been, could have been or could be converted into U.S. dollars at that or any other exchange rate as of that or any other date.

General Information

In this Annual Report on Form 20-F, or Annual Report, "Orchard,", the "company," "we," "us," and "our" refer to Orchard Therapeutics plc and its consolidated subsidiaries, except where the context otherwise requires.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report contains express or implied forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve substantial risks and uncertainties. In some cases, forward-looking statements may be identified 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 Annual Report are based upon information available to our management as of the date of this Annual Report, 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 Annual Report 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 our in-house manufacturing operations;
- the rate and degree of market acceptance and clinical utility of our commercial product and product candidates, in particular, and gene therapy, in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- our competitive position;
- the scope of protection we and/or our licensors are able to establish and maintain for intellectual property rights covering our commercial product and product candidates;
- developments and projections relating to our competitors and our industry;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- the impact of laws and regulations;
- our ability to attract and retain qualified employees and key personnel;
- our ability to contract with third party suppliers and manufacturers and their ability to perform adequately;
- 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 be assured that the forward-looking statements in this Annual Report 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, these statements should not be regarded 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 Annual Report and the documents that we reference in this Annual Report and have filed as exhibits to this Annual Report 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.

PART I

Item 1. Identity of Directors, Senior Management and Advisers

Not applicable.

Item 2. Offer Statistics and Expected Timetable

Not applicable.

Item 3. Key Information

A. Selected financial data.

The following tables present the selected consolidated financial data as of the dates and for the periods indicated for Orchard Therapeutics plc. We derived the selected consolidated statements of operations and comprehensive loss data for the years ended December 31, 2018, 2017, and 2016 and the consolidated balance sheet data as of December 31, 2018 and 2017 from our audited consolidated financial statements included elsewhere in this Annual Report. The consolidated balance sheet data as of December 31, 2016 is derived from our consolidated financial statements not included in this Annual Report.

Our historical results are not necessarily indicative of our future results. This data should be read together with our consolidated financial statements and related notes appearing elsewhere in this Annual Report.

Although we are a UK company, the functional currency of our reporting entity is the U.S. Dollar. Where the local currency of our subsidiaries is not 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 a component of shareholders' equity.

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

As of December 31, 2018, the last business day of the fiscal year ended December 31, 2018, the representative exchange rate was £1.00 = $1.2687.

te	Year Ended December 31,		
	2018	2017	2016
		(in thousands)	
Consolidated Statement of Operations and Comprehensive Loss Data:			
Product Sales, net	$ 2,076	$ —	$ —
Costs and operating expenses:			
Cost of product sales	422	—	—
Research and development	205,319	32,527	16,206
Selling, general and administrative	31,366	5,985	2,997
Total operating expenses	237,107	38,512	19,203
Loss from operations	(235,031)	(38,512)	(19,203)
Other income (expense), net	5,506	(1,179)	138
Net loss before income taxes	(229,525)	(39,691)	(19,065)
Income tax expense	(970)	(53)	(20)
Net loss attributable to ordinary shareholders	$ (230,495)	$ (39,744)	$ (19,085)
Other comprehensive (loss) income:			
Foreign currency translation adjustment	(964)	4,398	(271)
Total comprehensive loss	$ (231,459)	$ (35,346)	$ (19,356)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (10.22)	$ (4.48)	$ (2.69)
Weighted average number of ordinary shares outstanding, basic and diluted	22,559,389	8,872,768	7,100,528

	As of December 31,		
	2018	2017	2016
	(in thousands)		
Consolidated Balance Sheet Data:			
Cash	$ 335,844	$ 89,856	$ 3,497
Working capital(1)	307,612	83,466	163
Total assets	366,042	97,294	4,283
Convertible preferred shares in temporary equity	—	—	16,970
Total shareholders' (deficit) equity	311,338	86,405	(16,524)

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

B. Capitalization and indebtedness.

Not applicable.

C. Reasons for the offer and use of proceeds.

Not applicable.

D. Risk factors.

Our business faces significant risks. This section of the Annual Report highlights some of the risks that may affect our future operating results. You should carefully consider the risks described below, as well as in our consolidated financial statements and the related notes included elsewhere in this Annual Report and in our other SEC filings. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or growth prospects. This Annual Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in these forward-looking statements, as a result of certain factors including the risks described below and elsewhere in this Annual Report and our other SEC filings. See "Cautionary Statement Regarding Forward-Looking Statements" above.

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 $230.5 million, $39.7 million, and $19.1 million for the years ended December 31, 2018, 2017, and 2016, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares and sale of our ADSs in our initial public offering. 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-, 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 or technologies;
- 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 our own in-house manufacturing operations;
- 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
- comply with our obligations as 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. Our revenue from sales of Strimvelis alone will not 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.

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 recorded a liability for Strimvelis representing the fair value of the future expected costs to maintain the marketing authorization in excess of expected future sales. Our ability to generate future revenues from product sales depends heavily on our and or our collaborators' success in:

- completing research and preclinical development of our product candidates and identifying new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- launching and commercializing product candidates for which we obtain regulatory and marketing approval by expanding our existing sales force, marketing and distribution infrastructure or, alternatively, collaborating with a commercialization partner;
- maintaining marketing authorization and related regulatory compliance for Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Strimvelis and any product candidate for which we obtain marketing approval;
- establishing and maintaining supply and manufacturing processes and relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development of our product candidates and the market demand for Strimvelis and any of our product candidates for which we obtain marketing approval;

- obtaining market acceptance of Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and compliance systems;
- negotiating favorable terms in any collaboration, licensing or other arrangements into which we may enter and performing our obligations under such arrangements;
- maintaining, protecting and expanding our portfolio of intellectual property rights, including patents, trade secrets and know-how; and
- attracting, hiring and retaining qualified personnel.

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

We may 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, if such product candidates are approved, 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 out 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, 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 to raise 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 capital through the sale of equity, convertible debt securities or other equity-based derivative securities, ownership percentages of all our shareholders may be diluted and the terms may include liquidation or other preferences that adversely affect their rights as shareholders. 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 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 financing may not be available to us on acceptable terms, or at all.

Our limited operating history may make it difficult 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 (Europe) Limited, which was founded in 2015, and its subsidiaries. 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 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 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 guidance, 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 contract manufacturing organizations, or 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 Annual Report are current as of the dates specified and are preliminary in nature. Our company-sponsored clinical trials of OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS and the investigator-sponsored clinical trials for OTL-102 for X-CGD and OTL-300 for TDBT are ongoing and not complete. Success in preclinical studies or early clinical trials may not be indicative of results obtained in later trials.

From time to time, we may publish interim data and/or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as more

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

With respect to clinical trials conducted by our academic or other collaborators, such as UCL, UCLA and GSK, we may not have access to the most recent clinical data or the clinical data available to us may otherwise be limited or incomplete. Interim data or ad hoc analyses from these clinical trials are not necessarily predictive of final results. Interim data or ad hoc analyses are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and/or more patient data become available to us. Interim, topline and preliminary data and ad hoc analyses also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data available to us or that we previously published. As a result, preliminary and interim data and ad hoc analyses should be viewed with caution until the final data are available. Material adverse changes in the final data compared to the preliminary or interim data or ad hoc analyses could significantly harm our business prospects.

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

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

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

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

We plan to submit any data available to us from compassionate use cases as part of any regulatory submission for the applicable product candidate. However, because these patients were not treated as part of a clinical trial in accordance with the procedures set forth under the applicable clinical trial protocol, regulatory authorities may not accept compassionate use data as sufficient clinical validation in support of our regulatory approval efforts, or they may find that the data submitted from our clinical trials are insufficient to support approval. Such decisions could materially and adversely affect our business, financial condition, results of operations and prospects.

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

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

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

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

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

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

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

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

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

- delays in reaching a consensus with regulatory agencies on study design;
- delays in reaching agreement on acceptable terms with prospective CROs and clinical trial sites;
- delays in obtaining required IRB approval at each clinical trial site;
- delays in recruiting suitable patients to participate in our clinical trials;
- imposition of a clinical hold by regulatory agencies;
- failure by our academic partners, CROs, other third parties or us to adhere to clinical trial protocol and recordkeeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- the occurrence of SAEs associated with the product candidate that are viewed to outweigh its potential benefits; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

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

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

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

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

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

A rolling BLA is an application process that allows us to submit the information required by the BLA in sections. The FDA will not complete, and may delay initiating, its review of our BLA until we submit all of the required information for a full BLA. If we are delayed or unable to provide this required information it could delay or prevent our ability to obtain regulatory approvals, as a result of which our business, prospects, financial condition and results of operations may suffer.

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

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

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

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

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

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

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

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

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

We may be unable to demonstrate comparability between drug product manufactured using hematopoietic stem cells, or 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. We cannot be assured 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 be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval or our product candidates using these production methods and processes. For example, both the FDA and the EMA has advised us that it will require clinical data using drug product that has been cryopreserved as part of our planned BLA and MAA submissions for OTL-103 for WAS. In addition, we are conducting a clinical trial at UCLA using a cryopreserved formulation of OTL-101 (with bone marrow as the cellular source). In this trial, one of the 10 patients treated with this formulation failed to engraft, although we do not believe engraftment failure was due to use of a cryopreserved formulation.

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

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

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

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

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing such product candidate. We have not received approval to market any of our product candidates from regulatory authorities in any jurisdiction. We have only limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process.

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

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

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

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

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

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

In addition, the FDA has granted Rare Pediatric Disease designation to Strimvelis, OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-IIIA, and we may seek Rare Pediatric Disease designation for some of our other product candidates. The FDA defines a “rare pediatric disease” as a serious or life-threatening disease in which the serious of life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be received from sales in the U.S. of such drug. Under the FDA’s Rare Pediatric Disease Priority Review Voucher, or PRV, program, upon the approval of a BLA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a Rare Pediatric Disease PRV that can be used to obtain priority review for a subsequent new drug application or BLA. The PRV may be sold or transferred an unlimited number of times. Congress has extended the PRV program until September 30, 2020, with potential for PRVs to be granted until 2022. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for OTL-101 for ADA-SCID, OTL-200 for MLD, OTL-103 for WAS and OTL-201 for MPS-IIIA and qualify for such a PRV, the program may no longer be in effect at the time or the value of any such PRV may decrease such that we are may not be able to realize the benefits of such PRV.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The granting of a conditional marketing authorization is restricted to situations in which only the clinical part of the application is not yet fully complete. Incomplete preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

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

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

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

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

In addition, product manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance CGMP requirements and adherence to commitments made in the BLA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured or disagrees with the promotion, marketing or labeling of that product, a regulatory authority may impose restrictions relative to that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing.

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

- issue a warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;

- suspend any ongoing clinical trials;
- refuse to approve a pending BLA or comparable foreign marketing application (or any supplements thereto) submitted by us or our strategic partners;
- restrict the marketing or manufacturing of the product;
- seize or detain the product or otherwise require the withdrawal of the product from the market;
- refuse to permit the import or export of products; or
- refuse to allow us to enter into supply contracts, including government contracts.

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

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

Both marketing authorization holders and manufacturers of medicinal products are subject to comprehensive regulatory oversight by the EMA and the competent authorities of the individual European Union Member States both before and after grant of the manufacturing and marketing authorizations. This includes control of compliance with CGMP rules, which govern quality control of the manufacturing process and require documentation policies and procedures. We and our third-party manufacturers would be required to ensure that all of our processes, quality systems, methods, and equipment are compliant with CGMP. Failure by us or by any of our third-party partners, including suppliers, manufacturers, and distributors to comply with European Union laws and the related national laws of individual European Union Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

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

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

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

We rely primarily on know-how and trade secret protection for aspects of our proprietary technologies, our commercial product Strimvelis and our product candidates. We do not have any issued patents covering our commercial product Strimvelis or our product candidates, and only one patent family with patent applications pending in the United States and Europe with patent claims directed to our OTL-101 product candidate and its use in the treatment of ADA-SCID. This means that barriers to entry that typically apply in the case of pharmaceutical and biopharmaceutical companies with issued patents covering aspects of their proprietary technologies, products and product candidates, such as composition of matter claims, will generally not apply to our commercial product or our product candidates, and this may expose us to intense competition from other biopharmaceutical companies, particularly those companies that possess greater financial resources and more mature product candidate development, manufacturing, marketing and distribution resources than we do. Although our product candidates, if approved, may be eligible for marketing and/or data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial product or one or more of our product candidates, the result of which could have a material adverse effect on our business.

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

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. On December 13, 2018, we entered into a long-term lease agreement for our own gene therapy manufacturing facility in Fremont, California. We are in the process of building out this manufacturing facility to develop CGMP manufacturing capacity for both lentiviral vector and cryopreserved cell therapy products. 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 we or 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.

We are in the process of building out our Fremont, California manufacturing facility 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 lease for a 152,995 square foot facility located in Fremont, California to serve as an alternative or an addition to our reliance on CMOs, for the manufacture of our viral vectors and product candidates. We plan to renovate and customize this 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 previous 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 renovation and customization of our Fremont, California facility 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 in Fremont, California requires 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 renovate and operate our planned manufacturing facility could adversely affect the commercial viability of our product candidates.

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

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

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

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

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

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

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

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

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

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

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

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

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

Risks related to our reliance on third parties

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

We have entered into licensing and collaboration agreements with third parties, including the GSK Agreement, pursuant to which GSK transferred to us Strimvelis, OTL-200 for MLD, OTL-103 for WAS and OTL-300 for TDBT. In addition GSK novated to us their R&D and collaboration and license agreement, or the R&D Agreement, with Telethon-OSR. 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.

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

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

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

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

If our collaborations do not result in the successful development and commercialization of products, or if one of our collaborators terminates its agreement with us, we may not receive any future research funding or milestone or royalty payments under the collaboration. If we do not receive the funding we expect under these agreements, our development of product candidates could be delayed and we may need additional resources to develop our product candidates. In addition, if one of our collaborators terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of us in the business and financial communities could be adversely affected. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report 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 complete the build out of our Fremont, California manufacturing facility and establish that it has been properly commissioned to comply with CGMP requirements, we will not be able to independently manufacture material for our planned clinical programs or our commercial supply, Strimvelis or any other product for which we obtain marketing approval. We currently rely on our CMOs and in some cases academic partners for the production of our viral vectors and product candidates for our ongoing registrational and clinical trials and preclinical studies. For future clinical trials and for products for which we obtain marketing approval, we intend to utilize materials manufactured by CGMP-compliant CMOs. If our academic partners or these CMOs do not successfully carry out their contractual duties, meet expected deadlines or manufacture our viral vector and product candidates in accordance with regulatory requirements or if there are disagreements between us and our academic partners or these CMOs, we will not be able to complete, or may be delayed in completing, the preclinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or preclinical data. In such instances, we may need to enter into an appropriate replacement third-party relationship, which may not be readily available or available on acceptable terms, which would cause additional delay or increased expense prior to the approval of our product candidates and would thereby have a negative impact on our business, financial condition, results of operations and prospects.

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

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

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

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

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

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

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

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

clinical protocols or regulatory requirements, or for any other reasons, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, the EMA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure 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 any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

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

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

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

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

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

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

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

- the interruption of supply resulting from modifications to or discontinuation of a supplier's operations;
- delays in product shipments resulting from uncorrected defects, reliability issues, or a supplier's variation in a component;
- a lack of long-term supply arrangements for key components with our suppliers;
- the inability to obtain adequate supply in a timely manner, or to obtain adequate supply on commercially reasonable terms;
- difficulty and cost associated with locating and qualifying alternative suppliers for our components in a timely manner;
- production delays related to the evaluation and testing of products from alternative suppliers, and corresponding regulatory qualifications;
- a delay in delivery due to our suppliers prioritizing other customer orders over ours;

- damage to our reputation caused by defective components produced by our suppliers;
- increased cost of our warranty program due to product repair or replacement based upon defects in components produced by our suppliers; and
- fluctuation in delivery by our suppliers due to changes in demand from us or their other customers.

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

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

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

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

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

Risks related to commercialization of our product candidates

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

If our product candidates are approved for commercialization, we currently intend to seek to commercialize them in the United States and Europe directly with specialized teams, given the relative rarity of the indications we are targeting. We currently have a limited marketing and sales team for the marketing, sales and distribution of our commercial product and our product candidates, if approved. In order to commercialize Strimvelis and OTL-101 for ADA-SCID, OTL-200 for MLD and OTL-103 for WAS, if approved, or any of our other product candidates that may be approved, we must build, on a territory-by-territory basis, marketing, sales, distribution, managerial and other capabilities or make arrangements with third parties to perform these services, and we may not be successful in doing so.

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

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

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

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

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

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

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

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

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

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

- the potential efficacy and potential advantages over alternative treatments;
- the frequency and severity of any side effects, including any limitations or warnings contained in a product's approved labeling;
- the frequency and severity of any side effects resulting from the conditioning regimen or follow-up requirements for the administration of our product candidates;
- the relative convenience and ease of administration;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments; and
- sufficient third-party insurance coverage or reimbursement.

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

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

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

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

Outside the United States, certain countries, including a number of member states of the European Union, set prices and reimbursement for pharmaceutical products, or medicinal products, as they are commonly referred to in the European Union, with limited participation from the marketing authorization holders. We cannot be sure that such prices and reimbursement will be acceptable to us or our collaborators. If the regulatory authorities in these jurisdictions set prices or reimbursement levels that are not commercially attractive for us or our collaborators, our revenues from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. An increasing number of countries are taking initiatives to attempt to reduce large budget deficits by focusing cost-cutting efforts on pharmaceuticals for their state-run health care systems. These international price control efforts have impacted all regions of the world, but have been most drastic in the European Union. Additionally, some countries require approval of the sale price of a product before it can

be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. As a result, we might obtain marketing approval for a product in a particular country, but then may experience delays in the reimbursement approval of our product or be subject to price regulations that would delay our commercial launch of the product, possibly for lengthy time periods, which could negatively impact the revenues we are able to generate from the sale of the product in that particular country.

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

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

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

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

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Patient Protection and Affordable Care Act or the PPACA, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, was enacted, which, among other things, subjected biologic products to potential competition by lower-cost biosimilars; addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; subjected manufacturers to new annual fees and taxes for certain branded prescription drugs; and provided incentives to programs that increase the federal government’s comparative effectiveness research. Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. Further, since January 2017, President Trump signed two Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. One Executive Order directs 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. The second Executive Order terminates 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. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than $12 billion in ACA risk corridor payments to third-party payers who argued were owed to them. The effects of this gap in reimbursement on third-party payers, the viability of the ACA marketplace, providers, and potentially our business, are not yet known. 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." On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the ACA, and therefore, because it was repealed as part of the Tax Cuts and Jobs Act of 2017, or TCJA, the remaining provisions of the Affordable Care Act are invalid as well. While the Trump Administration and CMS have both stated that the ruling will have no immediate effect, and on December 30, 2018 the Texas District Court Judge issued an order staying the judgment pending appeal, it is unclear how this decision, subsequent appeals and other efforts to repeal and replace the ACA will impact the ACA and our business.

Additionally, on January 22, 2018, President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain ACA-mandated fees, including the so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain high cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device exercise tax on non-exempt medical devices. Further, the BBA, among other things, amends the ACA, effective January 1, 2019, to increase from 50 percent to 70 percent the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." Congress also could consider subsequent legislation to replace elements of the ACA that are repealed. Thus, the full impact of the ACA, any law replacing elements of it, and the political uncertainty surrounding any repeal or replacement legislation on our business remains unclear. In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013, and will remain in effect through 2027 unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012, was signed into law, which, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

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

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

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

Risks related to our business operations

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

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

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

- use of cash resources;
- higher than anticipated acquisition costs and expenses;
- potentially dilutive issuances of equity securities;
- the incurrence of debt and contingent liabilities, impairment losses or restructuring charges;
- large write-offs and difficulties in assessing the relative percentages of in-process research and development expense that can be immediately written off as compared to the amount that must be amortized over the appropriate life of the asset; and
- amortization expenses related to other intangible assets.

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

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

Our future success depends, in part, upon our ability to manage our expansion opportunities. Integrating new operations into our existing business in an efficient and timely manner, successfully monitoring our operations, costs, regulatory compliance and customer relationships, and maintaining other necessary internal controls pose substantial challenges for us. As a result, we cannot assure 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 have adopted a code of conduct applicable to all of our employees, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

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

Our operations are subject to anti-corruption laws, including the Bribery Act, the FCPA, the U.S. domestic bribery statute contained in 18 U.S.C. §201, the U.S. Travel Act, and other anti-corruption laws that apply in countries where we do business. The Bribery Act, the FCPA and these other laws generally prohibit us and our employees and intermediaries from authorizing, promising, offering, or providing, directly or indirectly, improper or prohibited payments, or anything else of value, to government officials or other persons to obtain or retain business or gain some other business advantage. Under the Bribery Act, we may also be liable for failing to prevent a person associated with us from committing a bribery offense. We and our commercial partners operate in a number of jurisdictions that pose a high risk of potential Bribery Act or FCPA violations, and we participate in collaborations and relationships with third parties whose corrupt or illegal activities could potentially subject us to liability under the Bribery Act, FCPA or local anti-corruption laws, even if we do not explicitly authorize or have actual knowledge of such activities. In addition, we cannot predict the nature, scope or effect of future regulatory requirements to which our international operations might be subject or the manner in which existing laws might be administered or interpreted.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- economic weakness, including inflation, or political instability in particular non-U.S. economies and markets;
- differing and changing regulatory requirements for product approvals;
- differing jurisdictions could present different issues for securing, maintaining or obtaining freedom to operate in such jurisdictions;
- potentially reduced protection for intellectual property rights;
- difficulties in compliance with different, complex and changing laws, regulations and court systems of multiple jurisdictions and compliance with a wide variety of foreign laws, treaties and regulations;
- changes in non-U.S. regulations and customs, tariffs and trade barriers;
- changes in non-U.S. currency exchange rates of the pound sterling, U.S. dollar, euro and currency controls;
- changes in a specific country's or region's political or economic environment, including the implications of the recent decision of the eligible members of the U.K. electorate for the United Kingdom to withdraw from the European Union;

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

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

In June 2016, a majority of the eligible members of the electorate in the United Kingdom voted to withdraw from the European Union in a national referendum, commonly referred to as Brexit. The withdrawal of the United Kingdom from the European Union will take effect either on the effective date of the withdrawal agreement or, in the absence of agreement, two years after the United Kingdom provides a notice of withdrawal pursuant to Article 50 of the EU Treaty, unless the European Council, in agreement with the United Kingdom, unanimously decides to extend this period. On March 29, 2017, the U.K. Prime Minister formally delivered the notice of withdrawal. The United Kingdom is, therefore, scheduled to leave the European Union at 11:00p.m. GMT on March 29, 2019. If the United Kingdom and the European Union are unable to negotiate acceptable withdrawal terms, barrier-free access between the United Kingdom and other European Member States or among the European Economic Area, or EEA, overall could be diminished or eliminated.

The uncertainty concerning the United Kingdom's legal, political and economic relationship with the European Union after Brexit may be a source of instability in the international markets, create significant currency fluctuations, and/or otherwise adversely affect trading agreements or similar cross-border co-operation arrangements (whether economic, tax, fiscal, legal, regulatory or otherwise) beyond the date of Brexit.

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. The long-term effects of Brexit will depend on any agreements (or lack thereof) between the United Kingdom and the European Union and, in particular, any arrangements for the United Kingdom to retain access to European Union markets either during a transitional period or more permanently.

Such a withdrawal from the European Union is unprecedented, and it is unclear how the United Kingdom's access to the European single market for goods, capital, services and labor within the European Union, or single market, and the wider commercial, legal and regulatory environment, will impact our United Kingdom operations. and customers. Our United Kingdom operations could be disrupted by Brexit, particularly if there is a change in the United Kingdom's relationship to the single market.

We may also face new regulatory costs and challenges that could have an adverse effect on our operations. Depending on the terms of the United Kingdom's withdrawal from the European Union, 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 the European Union and the EEA more difficult. Furthermore, there are likely to be changes to the way in which marketing approvals are granted in the United Kingdom, which could add time and expense to the process by which our product candidates receive and maintain regulatory approval in the United Kingdom and across the EEA in the future. Even prior to any change to the United Kingdom's relationship with the European Union, the announcement of Brexit has created economic uncertainty surrounding the terms of Brexit and its consequences which could adversely affect our business, revenue, financial condition, results of operations and could adversely affect the market price of our ADSs.

We 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.

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

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

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

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

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

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

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

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the licensor may have the right to terminate the agreement. Disputes may arise between us and any of our licensors regarding intellectual property subject to such agreements and other issues. Such disputes over intellectual property that we have licensed or the terms of our license agreements may prevent or impair our ability to maintain our current arrangements on acceptable terms, or at all, or may impair the value of the arrangement to us. Any such dispute could have a material adverse effect on our business. If we cannot maintain a necessary license agreement or if the agreement is terminated, we may be unable to successfully develop and commercialize the affected products and product candidates. Termination of our license agreements or reduction or elimination of our rights under them may result in our having to negotiate a new or reinstated agreement, which may not be available to us on equally favorable terms, or at all, which may mean we are unable to develop or commercialize the affected product or product candidate or cause us to lose our rights under the agreement. Any of the foregoing could have a material adverse effect on our business

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

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

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

We currently do not own any issued patents related to our products and product candidates. Certain intellectual property related to Strimvelis and all of our product candidates are in-licensed from third parties but we have not in-licensed any issued patents related to Strimvelis or any of our product candidates. In certain situations and as considered appropriate, we and our licensors have sought, and we intend to continue to seek to protect our proprietary position by filing patent applications in the United States and, in at least some cases, one or more countries outside the United States relating to current and future products and product candidates that are important to our business. However, we cannot predict whether the patent applications currently being pursued will issue as patents, whether the claims of any resulting patents will provide us with a competitive advantage or prevent competitors from designing around our claims to develop competing technologies in a non-infringing manner, or whether we will be able to successfully pursue patent applications in the future relating to our current or future products and product candidates. Moreover, the patent application and approval process is expensive and time-consuming. We may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. Furthermore, we, or any future partners, collaborators, or licensees, may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection on them. Therefore, we may miss potential opportunities to seek additional patent protection.

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

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

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

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

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

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

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

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable or that we elect not to patent, processes for which patents are difficult to enforce and any other elements of our product candidate discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. However, trade secrets can be difficult to protect and some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our employees, consultants, scientific advisors, and contractors. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach.

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

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

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

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

We or our licensors may be subject to claims that former employees, collaborators or other third parties have an ownership interest in the patents and intellectual property that we own or license or that we may own or license in the future. While it is our policy to require our employees and contractors who may be involved in the development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who in fact develops intellectual property that we regard as our own or such assignments may not be self-executing or may be breached. Our licensors may face similar obstacles. We could be subject to ownership disputes arising, for example, from conflicting obligations of employees, consultants or others who are involved in developing our products or product candidates. Litigation may be necessary to defend against any claims challenging inventorship or ownership. If we or our licensors fail in defending any such claims, we may have to pay monetary damages and may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property, which could adversely impact our business, results of operations and financial condition.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

- we may not develop additional proprietary technologies that are patentable; and
- we or our licensors or collaborators may choose not to file a patent application for certain trade secrets or know-how, and a third party may subsequently file a patent application or obtain a patent covering such intellectual property.

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

Risks related to ownership of our securities

The market price of our ADSs may be highly volatile, and may fluctuate due to factors beyond our control. An active public trading market for our ADSs may not be sustained.

We completed our initial public offering in November 2018. Prior to that time, there was no public trading market for our ADSs or ordinary shares. Although we have completed our initial public offering and our ADSs are listed and trading on the Nasdaq Global Select Market, an active trading market for our ADSs may not be sustained. If an active market for our ADSs is not sustained, it may be difficult for existing shareholders to sell our ADSs without depressing the market price for our securities or at all. An inactive trading market may also impair our ability to raise capital to continue to fund operations by selling ADSs and may impair our ability to acquire other companies or assets by using our ADSs as consideration.

In addition, the trading price of our ADSs has fluctuated, and is likely to continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control. In addition to the factors discussed in this "Item 3.D.—Risk factors" and elsewhere in this Annual Report, these factors include:

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

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

We could be subject to securities class action litigation.

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

If securities or industry analysts do not continue to 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 depends 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. In the event 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.

Based upon our ordinary shares outstanding as of December 31, 2018, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 66.4% of our ordinary shares and ADSs. 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 our shareholders may believe are in their best interest as shareholders. Some of these persons or entities may have interests that are different than those of our other shareholders. For example, because many of these shareholders purchased their ordinary shares at prices substantially below the price at which ADSs were sold in our initial public offering 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.

Additional sales of our ADSs, or the perception that these sales could occur, could cause the market price of our ADSs to decline. If any of our large shareholders or members of our management team sell substantial amounts of ADSs in the public market, or the market perceives that such sales may occur, the market price of our ADSs and our ability to raise capital through an issue of equity securities in the future could be adversely affected.

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

Holders of our publicly-traded securities are holders 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.

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

ADSs are transferable on the books of the depositary. However, the depositary may close its books at any time or from time to time when it deems expedient in connection with the performance of its duties. The depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary think it is advisable to do so because of any requirement of law, government or governmental body, or under any provision of the deposit agreement, or for any other reason, subject to the right of ADS holders to cancel their ADSs and withdraw the underlying ordinary shares. Temporary delays in the cancellation of the holder's ADSs and withdrawal of the underlying ordinary shares may arise because the depositary has closed its transfer books or we have closed our transfer books, the transfer of ordinary shares is blocked to permit voting at a shareholders' meeting or we are paying a dividend on our ordinary shares. In addition, ADS holders may not be able to cancel their ADSs and withdraw the underlying ordinary shares when they owe money for fees, taxes and similar charges and when it is necessary to prohibit withdrawals in order to comply with any laws or governmental regulations that apply to ADSs or to the withdrawal of ordinary shares or other deposited securities.

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

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

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

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

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

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

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

Holders of our ADSs do 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 the holder's right to vote.

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

Holders of our ADSs 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 the holders of our ADSs 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. Holders of our ADSs will receive these distributions in proportion to the number of our ordinary shares such holder's 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 holders of our ADSs 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. These restrictions may have an adverse effect on the value of our ADSs.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be the sole source of gains to the holders of our ADSs and such holders may never receive a return on their 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 the sole source of gains to the holders of our ADSs for the foreseeable future, and such holders may suffer a loss on their investment if they are unable to sell their ADSs at or above the price at which such holders purchased the ADSs.

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. As of December 31, 2018, we have outstanding 85,865,557 ordinary shares. Of these shares, 69,761,485 shares currently are restricted as a result of securities laws or lock-up agreements but will be able to be sold in the future. Moreover, holders of an aggregate of approximately 60,168,900 ordinary shares 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, 10,203,432 ordinary shares reserved for issuance upon the exercise of existing options outstanding as of December 31, 2018 under our current equity incentive plans will become eligible for sale in the public market in the future, subject to certain legal and contractual limitations.

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 sold in our completed initial public offering and 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 holders of our ADSs to sell such ADSs at a time and price that they deem appropriate.

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 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 are not 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 completing our initial public 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 early as 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 our initial public 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 in our public filings with the SEC. We have taken advantage of reduced reporting burdens in this Annual Report. 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 continue to incur increased costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management is 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 have incurred and will continue to 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 are required to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations have increased and will continue to increase our legal and financial compliance costs and make some activities more time-consuming and costly.

Pursuant to Section 404, we are 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 are not 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 have engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we continue to dedicate internal resources, have engaged outside consultants and adopted a detailed work plan to assess and document the adequacy of internal control over financial reporting, taken steps to improve control processes as appropriate, validated through testing that controls are functioning as documented and have implemented 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 is 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 following our completed initial public offering. 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 previously identified material weaknesses in our internal control over financial reporting. We may identify future 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.

Prior to the completion of our initial public offering in November 2018, we were a private limited company, and as such, had not 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 a lack of sufficient processes, controls, and other review procedures performed by personnel familiar with U.S. GAAP during these periods. Specifically, the findings related 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.

In response to the material weaknesses, we hired a full-time Chief Financial Officer in January 2018, and we have hired additional finance and accounting personnel with appropriate expertise to perform specific functions, and design and implement improved processes and internal controls, build our financial management and reporting infrastructure and further develop and document our accounting policies and financial reporting procedures, including ongoing senior management review and audit committee oversight. We believe the finance and accounting personnel we hired have the required skills and capabilities. We have also enhanced our processes and accounting methodology related to the recognition and accrual of research and development expenses and reimbursements. We have also developed and enhanced our procedures with respect to our analysis of complex, non-routine transactions.

We have made significant progress to enhance our in-house accounting and finance function and developed more formalized procedures and processes to ensure the completeness and accuracy of our recognition of and accrual of research and development related expenses and reimbursements. This material weakness was identified during the preparation of the financials for the IPO, and due to the limited amount of time since then, we concluded that the material weakness associated with recognition and accrual of research and development related expenses and reimbursements had not yet been fully remediated as of December 31, 2018. We believe we have remediated the previously identified material weakness associated with the recognition of assets and liabilities contingent on future events.

More generally, if we are unable to meet the demands that have been placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, we may be unable to accurately report our financial results in future periods, or report them within the timeframes required by law or stock exchange regulations. Failure to comply with the Sarbanes-Oxley Act, when and as applicable, could also potentially subject us to sanctions or investigations by the SEC or other regulatory authorities. Any failure to maintain or implement required new or improved controls, or any difficulties we encounter in their implementation, could result in additional material weaknesses or significant deficiencies, cause us to fail to meet our reporting obligations or result in material misstatements in our financial statements. Furthermore, if we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed, and investors could lose confidence in our reported financial information. 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.

We are 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.

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 2018 taxable year, however, and we may become a CFC in a subsequent taxable year. 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 2018 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.

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.

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, 2018, we had cumulative carryforward tax losses of $155.2 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. Our eligibility to claim payable research and development tax credits may be limited or eliminated because we may no longer qualify as a small or medium-sized company. We may benefit in the future from the United Kingdom’s “patent box” regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the U.K. research and development tax credit regime or the “patent box” regime, or for any reason we are unable to qualify for such advantageous tax legislation, or we are unable to use net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments then our business, results of operations and financial condition may be adversely affected.

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

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

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

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

We are incorporated under English law. The rights of holders of ordinary shares and, therefore, certain of the rights of holders of ADSs, are governed by English law, including the provisions of the U.K. Companies Act 2006, or the Companies Act, and by our Articles of Association. These rights differ in certain respects from the rights of shareholders in typical U.S. corporations.

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

Item 4. Information on the Company

A. History and development of the company.

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. Pursuant to a corporate reorganization in connection with our initial public offering, all of the interests in Orchard Therapeutics Limited were exchanged for the same number and class of newly issued shares of Orchard Rx Limited and, as a result, Orchard Therapeutics Limited became a wholly owned subsidiary of Orchard Rx Limited. 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. On November 1, 2018, our different classes of preferred shares and our ordinary shares were consolidated on a one-for-0.8003 basis. Accordingly, all share, per share, and share option amounts for all periods presented in this Annual Report and the accompanying consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the reverse share split.

Following the share consolidation, each share was re-designated as an ordinary share on a one-for-one basis, and we completed our initial public offering of American Depositary Shares, or ADSs, on the Nasdaq Global Select Market. Our ADSs are traded under the symbol ORTX. Our ordinary shares are not listed.

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 Annual Report, and investors should not consider any information on, or that can be accessed through, our website as part of this Annual Report.

Our agent for service of process in the United States is Cogency Global, 10 East 40th Street, 10th Floor, New York, NY 10016.

Our actual capital expenditures for the years ended December 31, 2018, 2017 and 2016 amounted to $4.0 million, $1.6 million and $0.2 million, respectively. These capital expenditures primarily consisted of lab equipment and computer and office equipment. We expect our capital expenditures to increase in absolute terms in the near term as we continue to advance our research and development programs and grow our operations, including the build-out of our manufacturing facility. We anticipate our capital expenditures in 2019 to be financed from the proceeds from our existing cash and cash equivalents, including the net proceeds from our completed initial public offering.

B. Business overview

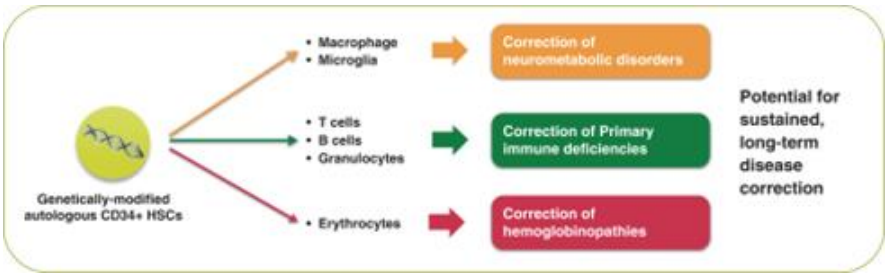
We are a commercial-stage, fully-integrated biopharmaceutical company dedicated to transforming the lives of patients with serious and life-threatening rare diseases through autologous *ex vivo* gene therapies. Our gene therapy approach seeks to transform a patient's own, or autologous, HSCs into a gene-modified 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.

We believe our commercial product and clinical-stage product candidates, 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. 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.

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.

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 Annual Report, 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.

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 have leased a facility in Fremont, California to accommodate our expanding technical operations and implement in-house drug product and vector manufacturing capabilities.

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

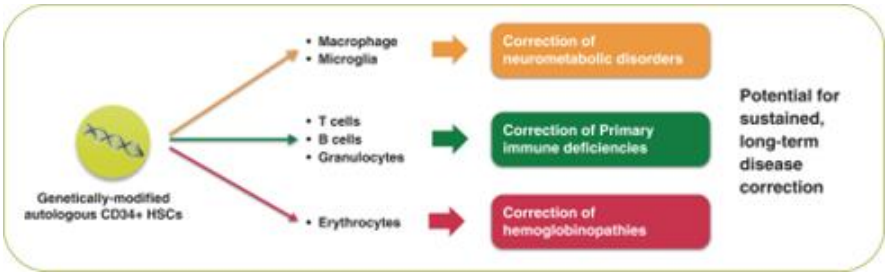
We have global commercial rights to Strimvelis and all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including the United States and Europe, subject to obtaining necessary marketing approvals in those jurisdictions. We plan to deploy a focused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

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

Our autologous *ex vivo* gene therapy approach

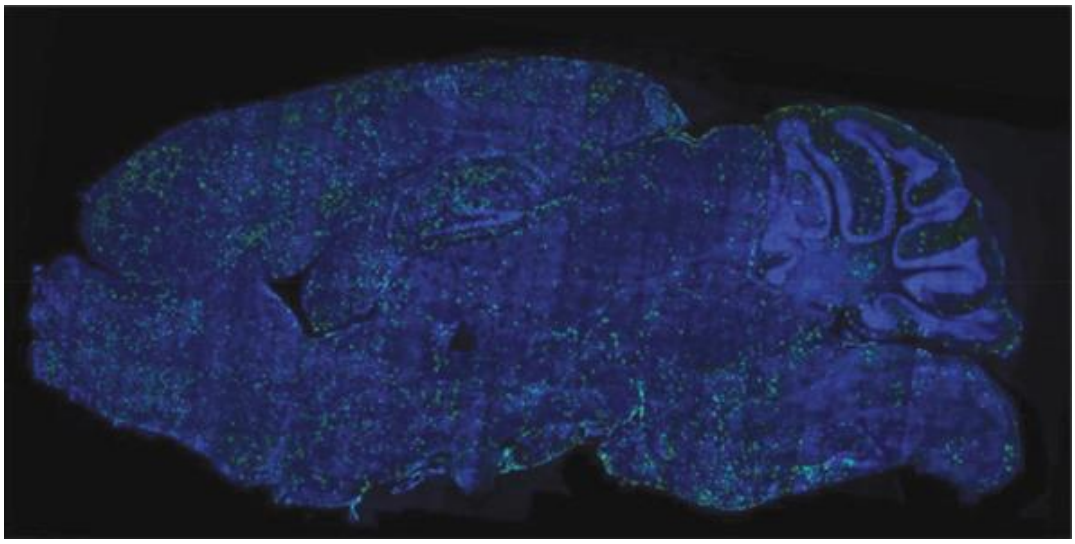
Our *ex vivo* gene therapy approach seeks to transform a patient's autologous HSCs into a gene-modified drug product to treat the patient's disease. HSCs are self-renewing cells that are capable of differentiating into all types of blood cells, including white blood cells, red blood cells and platelets.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

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



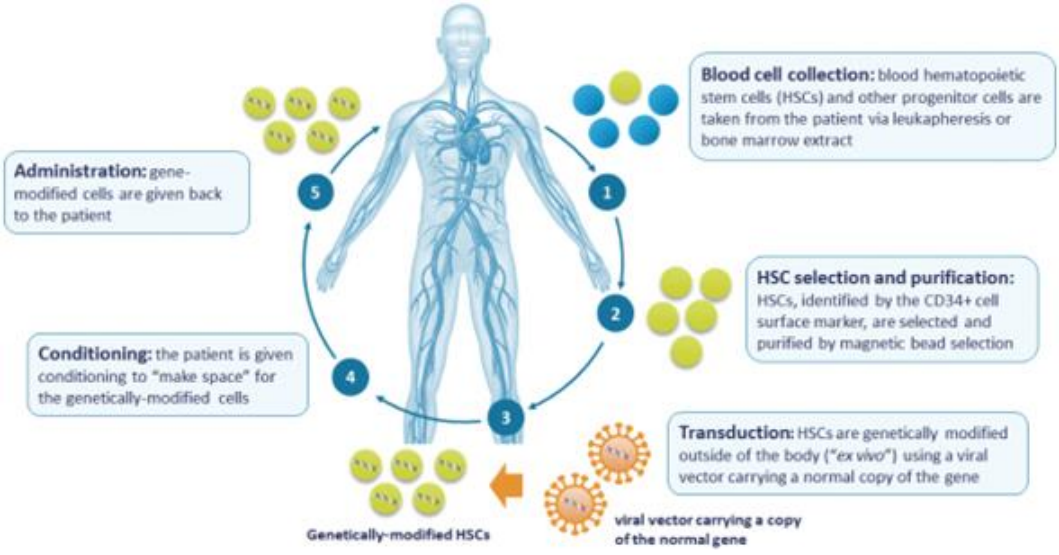
One example of the potential of our autologous *ex vivo* gene therapy approach to deliver genes to different physiological systems is demonstrated below. In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America*, or *PNAS*, a subpopulation of gene-modified HSCs have evidenced the potential to cross the blood-brain barrier, engraft in the brain as microglia and express genes and proteins within the central nervous system. As published in *PNAS*, the image below shows a cross-section of the brain of a mouse that received green fluorescent protein, or GFP, gene-modified HSCs intravenously. The GFP expression observed throughout the brain denotes the potential of gene-modified HSCs to cross the blood-brain barrier and express the functional protein throughout the brain, thereby potentially addressing a range of indications that affect the central nervous system. Our OTL-200 program for MLD leverages this same mechanism of action to deliver gene-modified HSCs through the blood-brain barrier and deliver a therapeutic gene that can prevent neuronal degeneration.

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



With respect to each of our product candidates, our *ex vivo* gene therapy approach utilizes a non-replicating lentiviral vector to introduce a functional copy of the missing or faulty gene into the patient's autologous HSCs through an *ex vivo* process called transduction, resulting in drug product that can then be re-introduced into the patient. Unlike other viral vectors, such as adeno-associated viral, or AAV, vectors, lentiviral vectors integrate into the chromosomes of patients' HSCs. We believe this allows us to achieve stable integration of the modified gene into the HSCs and to achieve durable expression of the target protein by the gene-modified HSCs after a single administration of gene therapy. Strimvelis, our commercial-stage product, utilizes an older generation gammaretroviral vector.

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



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

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

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

Our 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
- **L**everage the power of our therapeutic approach to expand our product pipeline across multiple indications
- Establish an efficient and scalable manufacturing infrastructure
- Establish a patient-centered, global commercial infrastructure
- Execute a disciplined business development strategy to strengthen our portfolio of product candidates

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. 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.

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 Annual Report, 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 February 2019, 62 patients have been treated with OTL-101 drug product, with a maximum follow-up of up to approximately 6 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 a clinical trial of 10 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 22 patients treated as of February 2019 represent compassionate use patients or patients for whom we do not have adequate follow-up as of the date of this Annual Report but for which safety data is presented in the summary below. Among the 62 patients treated so far, three patients, including one patient in the supportive UCLA trial, one patient in the additional GOSH trial and one in the compassionate use program, did not engraft and had to resume enzyme replacement therapy and/or receive rescue bone marrow transplant.

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

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

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

Ongoing registrational, supportive and additional clinical trials

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

Registrational trial at UCLA

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

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

Overall survival and event-free survival of 100% was observed at 12 months post-treatment, the primary endpoint of the trial. None of the enrolled patients required rescue medication, HSCT, or resumption of ERT. Importantly, patients in this trial showed immune cell reconstitution following treatment with OTL-101, which can lead to restoration of both cellular and humoral immune responses. This is reflected by the patients' ability to recover from infections beginning in the first six months following treatment. As of April 2017, the number of infections in evaluable patients decreased from 17 in the first year following treatment with OTL-101 to seven in the second year following treatment, and the number of serious infections in evaluable patients decreased from seven to one during the same period.

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

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

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

Overall Survival (OS) at 12 months (primary endpoint)

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (83.16, 100)	-
HSCT without MRD	85.71% (57.19, 98.22)	14.29% (-5.40, 42.81)
HSCT with MRD	100% (73.54, 100)	-
All HSCT	92.31% (74.87, 99.05)	7.69% (-10.08, 25.13)

Overall Survival (OS) at 12 months

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (78.20, 100)	-
HSCT without MRD	85.71% (57.19, 98.22)	14.29% (-8.99, 42.81)
HSCT with MRD	90.91% (58.72, 99.77)	9.09% (-14.24, 41.28)
All HSCT	88% (68.78, 97.45)	12.00% (-12.18, 31.56)

As summarized in the chart below, event-free survival is defined as survival without resumption of PEG-ADA enzyme replacement therapy or need for rescue allogeneic HSCT. Event-free survival in the OTL-101 treatment group was 100% at 12 months and at 24 months. In comparison, event-free survival in the combined allogeneic HSCT group was 80.77% (95% CI: 60.7-93.5%) at 12 months and 56% (95% CI: 34.9-75.6%) at 24 months. For the primary comparator group, who received allogeneic HSCT without a matched related donor, event-free survival rates were 35.71% lower (95% CI: 11.21-64.86%) and 50% lower (95% CI: 20.70-76.96%) than the OTL-101 treated group at 12 months and 24 months, respectively. Because the 95% confidence intervals for these estimates of the difference from the OTL-101 treated group do not include zero, these are statistically meaningful differences between the OTL-101 treated group and the HSCT without a matched related donor comparator group. Similarly, event-free survival in the comparator HSCT group that received a matched related donor (the current standard of care) was 36.36% lower (95% CI: 7.31-69.21%) than the OTL-101 treated group at 24 months. Because the 95% confidence intervals for this estimate does not include zero, this also represents a statistically meaningful difference between the OTL-101 treated group and the comparator HSCT with a matched related donor.

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

Event Free Survival (EFS) at 12 months (primary endpoint)

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (83.16, 100)	-
HSCT without MRD	64.29% (35.14, 87.24)	35.71% (11.21, 64.86)
HSCT with MRD	100% (73.54, 100)	-
All HSCT	80.77% (60.65, 93.45)	19.23% (0.71, 39.35)

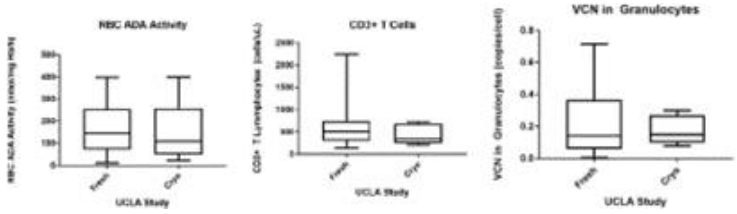
Event Free Survival (EFS) at 24 months

	Overall Survival (95% CI)	Reduction from OTL-101 group (95% CI)
OTL-101 pivotal data	100% (78.20, 100)	-
HSCT without MRD	50% (23.04, 76.96)	50% (20.70, 76.96)
HSCT with MRD	63.64% (30.79, 89.07)	36.36% (7.31, 69.21)
All HSCT	56% (34.93, 75.60)	44% (16.15, 65.07)

Ongoing supportive clinical trial with UCLA (with cryopreserved formulation)

A cryopreserved formulation of OTL-101 (with bone marrow as cellular source) is currently being evaluated in an ongoing supportive clinical trial at UCLA. Enrollment for this trial is complete; 10 patients have been treated, of which 9 have reached 12 months of follow-up; and 6 have reached 18 months of follow-up, as of January 2019. One patient treated in this trial withdrew since they 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, based on predictive criteria at six months 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 February 2019, six patients have been treated and are alive and off of ERT.

OTL-101 Program Safety

As of February 2019, 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. After completion of the database lock and review of data quality and consistency with industry practices, there were 27 SAEs reported, of which 1 was assessed by the investigator as being possibly related to protocol treatment or procedures. This SAE was a staphylococcal infection from the patient's transduced bone marrow cells. The patient was treated with antibiotics and recovered. The most common SAEs were 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 Annual Report, we have not been notified by the investigator in this clinical trial of any SUSAR.

As of February 2019, safety data from the 10 patients treated in the supportive clinical trial with UCLA in the United States and from two compassionate use patients, one of which received a fresh formulation and the other received a cryopreserved formulation, indicate OTL-101 was generally well-tolerated, with no instances of insertional mutagenesis. After ongoing quality review of the data, there were 8 SAEs reported in the supportive clinical trial with UCLA. 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 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 Annual Report, we have not been notified by the investigator of any SUSAR.

In Europe, as of February 2019, 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 possibly related to the protocol treatment, 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. This SAE was a staphylococcal infection, possibly resulting from a bacterial growth noted in samples of the fresh drug product taken during the transduction procedure at this academic facility. The most common SAEs across this 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 Annual Report, we have not been notified by the investigator of any SUSAR. In an ongoing cryopreserved study in the United Kingdom, where six of ten patients have been treated, there were eight SAEs reported, none of which were deemed to be related to the drug product. In three patients treated under compassionate use with cryopreserved formulation, fifteen 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 report for our registrational trial, and 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. During

our pre-BLA and subsequent dedicated CMC type B meetings in late 2018, we confirmed with FDA requisite data necessary to support the BLA. This data includes analytical comparability between academic and commercial manufacturing processes, vector and drug product process characterization as well as vector and drug product manufacturing state of control and/or process validation. We will initially seek approval of OTL-101 using patient bone marrow as cellular source material and subsequently seek approval for the use of mobilized peripheral blood, as alternative cellular source material. Although we currently expect to submit our BLA by 2020, our discussions with the FDA are ongoing and the definitive feedback from the FDA on the adequacy of the data to support an approval will continue to be a reviewed. 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, or 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 February 2019, a total of 33 patients have been treated with OTL-200 drug product, with a maximum follow-up of approximately eight and a half years post treatment, comprised of 20 patients in our registrational trial with a fresh product formulation, four 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 was transferred to us during the third quarter 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.

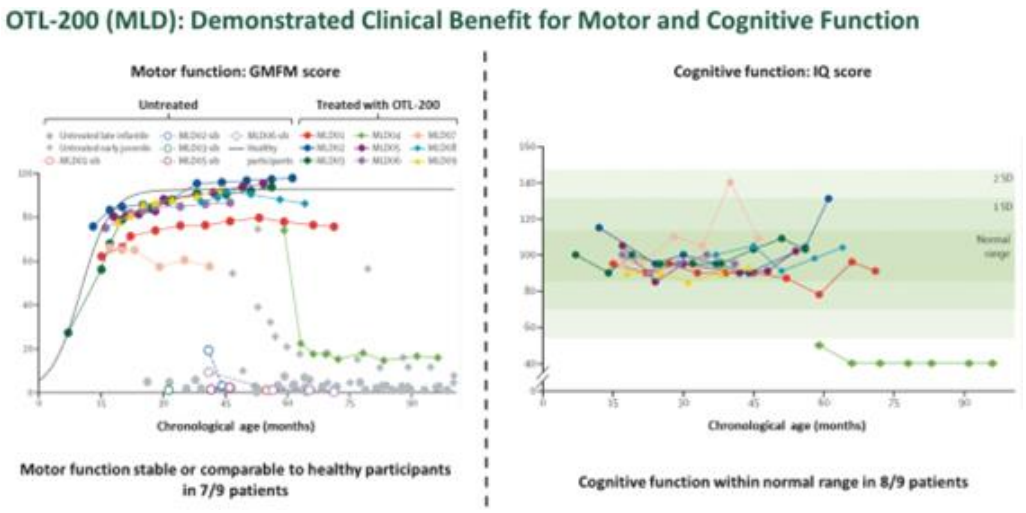
Registrational trial

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, both the late-infantile and early-juvenile patient groups 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 and mobilized peripheral blood 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 through 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.

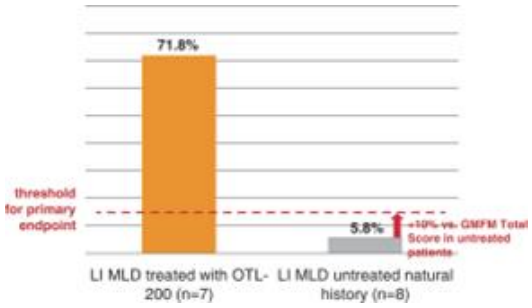
In this interim analysis, eight patients treated with OTL-200, seven of whom received treatment when pre-symptomatic, had prevention of disease onset or halted disease progression, as compared with patients in the natural history group, most of whom experienced rapid disease progression. In addition,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



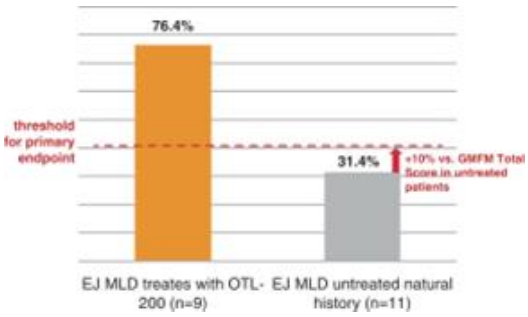
Presented below are efficacy data from a more recent interim analysis of all 20 patients treated in this clinical trial as of December 2017, the date of the most recent interim efficacy data report available to us. Motor function was measured in this trial with a GMFM score, which measures a child's 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 rapid disease progression that was deemed to be unrelated to the treatment. 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. 37 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 February 2019, nine patients were treated under compassionate use and ten SAEs have been 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. One patient treated under compassionate use died 12 months after treatment due to an unrelated cerebral stroke. Because follow-up is ongoing, safety data are preliminary and subject to change. As of the date of this Annual Report, 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 four patients treated as of February 2019 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.

Four patients have been treated in this trial as of February 2019. All patients tolerated the administration well and for those with enough follow-up post-treatment, evidence of engraftment and supraphysiological production of ARSA activity has been shown. To date, four SAEs have been reported in this study, none of which were considered related to the gene therapy.

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 pre-MAA meeting with the EMA, Rapporteur/Co-Rapporteur 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 pediatric 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 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 reached three years' follow-up by the end of September 2018. Manufacture of the fresh OTL-103 drug product formulation (with bone marrow or mobilized peripheral blood as the cellular source) was performed by a third-party commercial CMO. Data from the registrational trial will be supported by eight patients dosed in a compassionate use program. Based on discussions with the EMA, we intend to submit data to the EMA from additional patients treated with a cryopreserved formulation.

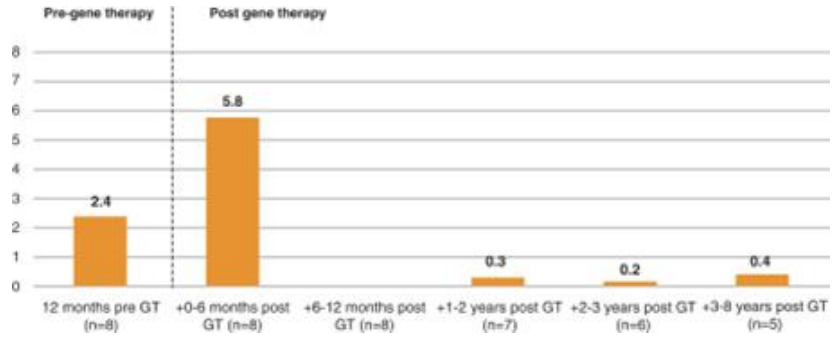
Patients treated in the registrational trial and compassionate use program were below the age of 12 years with a diagnosis of severe, classical WAS and were ineligible for HSCT treatment due to the absence of an HLA-matched sibling or family member to serve as an allogenic bone marrow donor.

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

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

OTL-103 (WAS): reduced frequency of severe infections

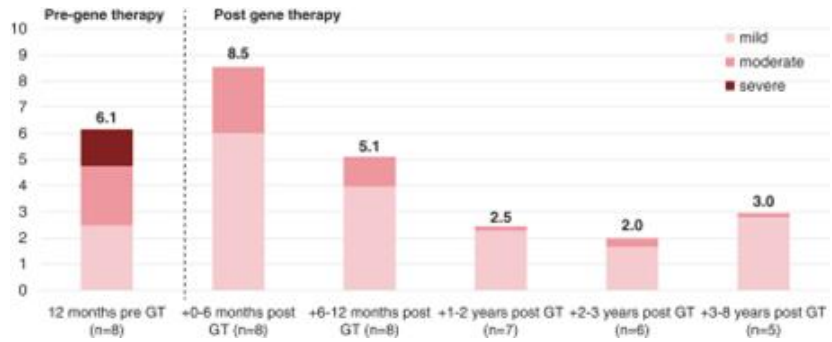
Severe infections per person/year



Mean platelet counts before treatment were low, with a range of 6–25 x 10^9 per liter observed in all eight patients. Platelet counts progressively improved in all patients. One year post-treatment platelet counts increased in all patients to a range of 21–74 x 10^9 per liter, and further increases in platelet count were observed in six patients to a range of 27–169 x 10^9 per liter at three years post-treatment. In addition to the increase in platelet count, increased and sustained platelet volume in seven patients was also observed at three years post-treatment. These increases in platelet count and volume resulted in reduced frequency and severity of bleeding events as compared to those experienced by these patients prior to treatment with OTL-103 as shown in the graph below.

OTL-103 (WAS): reduced frequency and severity of bleedings

Bleedings per person/year



As of February 2019, 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 8.6 years and a median follow-up of 6.5years. 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. 13 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 compassionate use patient died as a consequence of a deterioration in a pre-existing neurological condition. 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 and infections. 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 Annual Report, 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 HSCs derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product.”

Gene therapy for X-CGD

Disease overview

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

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

Limitations of current therapies

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

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

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

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

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

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

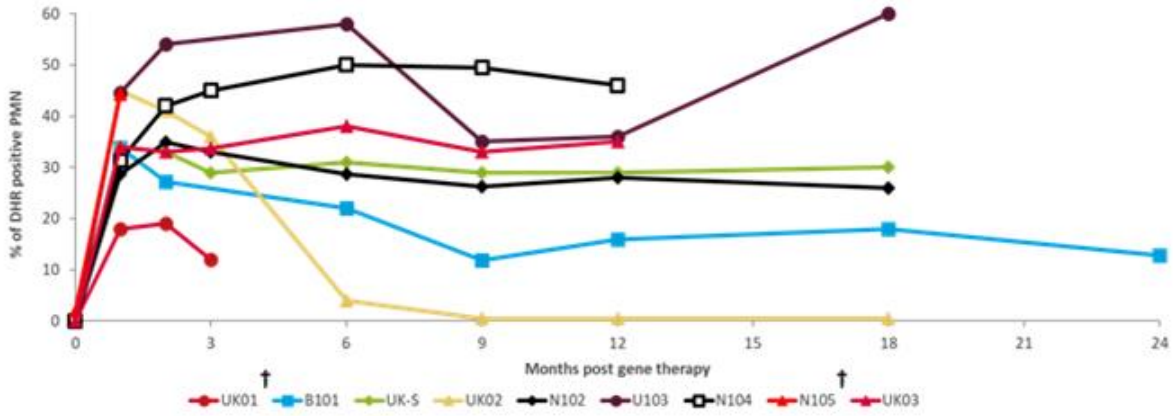
Ongoing clinical trials

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

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

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

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



(1) Excludes data from one patient treated with drug product deemed by the investigator to be a different form of OTL-102 drug product.

† Patient deceased from advanced disease.

As of February 2019, 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 twelve months post-treatment. There were nine 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 Annual Report, 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 February 2019, OTL-300 has been evaluated in a total of nine patients, the majority of which have a severe genotype of TDBT, including ß0/ß0, in an ongoing clinical trial at San Raffaele Hospital in Milan, Italy, with follow-up of up to approximately three years. The clinical trials for this program are being conducted under an investigator-sponsored CTA.

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

Ongoing clinical trials (cryopreserved formulation)

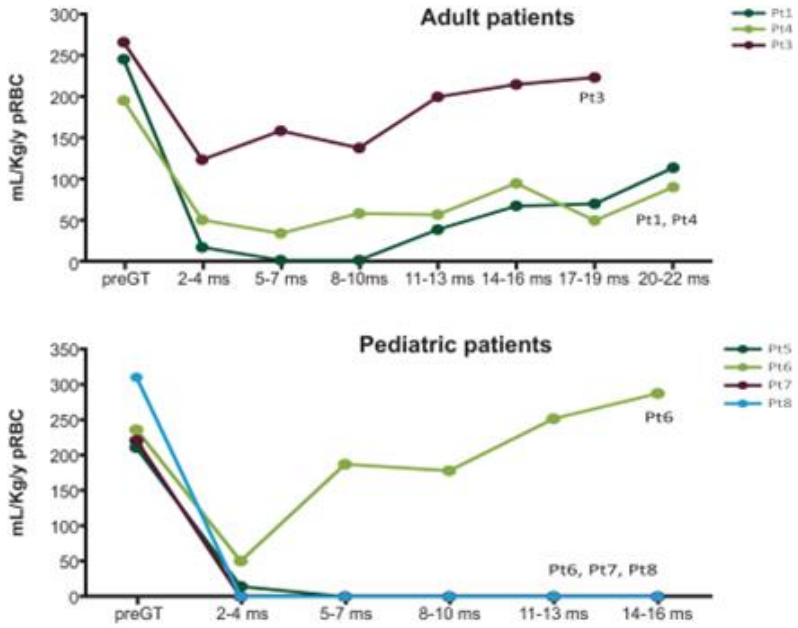
OTL-300 is currently being investigated in an ongoing academic-sponsored clinical trial at the San Raffaele Hospital in Milan, Italy to establish proof of concept. The target enrollment in this trial is nine patients with TDBT, and all nine patients have received a single dose of a cryopreserved formulation 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 December 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 central line and mycobacterium infection, febrile neutropenia, gastroenteritis, and obstructive pancreatitis due to gall stones. 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 Annual Report, we have not been notified by the investigator in this clinical trial of any SUSAR.

Preclinical data for our gene therapy programs

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

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

Disease overview

MPS-IIIA and MPS-IIIB are life-threatening metabolic diseases that cause accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within one to two years after birth, MPS-IIIA and MPS-IIIB patients experience progressive neurological decline, including speech delay and eventual loss of language, behavioral disturbances, and potentially severe dementia. Ultimately, most patients with MPS-IIIA progress to a vegetative state. Life expectancy for patients with MPS-IIIA and MPS-IIIB is between 10 to 25 years and 15 to 30 years, respectively.

The incidence of MPS-IIIA and MPS-IIIB are currently estimated to be one in 100,000 and one in 200,000 live births per year, respectively.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MPS-IIIA and MPS-IIIB. Palliative care options involve medications for seizures and pain, antibiotics and sedatives, on a case-by-case basis, as well as physiotherapy, hydrotherapy and tube feeding or gastrostomy when patients can no longer eat without assistance. Palliative care addresses the symptoms of MPS-IIIA and MPS-IIIB but does not slow or reverse the progression of the underlying disease. HSCT is not considered to be effective treatment options for these diseases. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MPS-IIIA and MPS-IIIB patients, their caregivers and families and healthcare systems.

Our Solution, OTL-201 for MPS-IIIA and OTL-202 for MPS-IIIB

We are developing OTL-201 and OTL-202 as autologous *ex vivo* gene therapies for treatment of patients with MPS-IIIA and MPS-IIIB, respectively. In both indications we believe preclinical studies in mice have shown that autologous *ex vivo* gene therapy has the potential to address the neurological manifestations of MPS-IIIA and MPS-IIIB. We plan to submit a CTA with the applicable regulatory authority in Europe for MPS-IIIA by the end of 2019 and plan to continue to progress preclinical development of MPS-IIIB.

We have obtained worldwide development and commercialization rights to OTL-201 for treatment of MPS-IIIA and OTL-202 for treatment of MPS-IIIB from The University of Manchester.

OTL-201 has received orphan drug designation from the EMA and FDA for the treatment of MPS-IIIA and has received rare pediatric disease designation from the FDA.

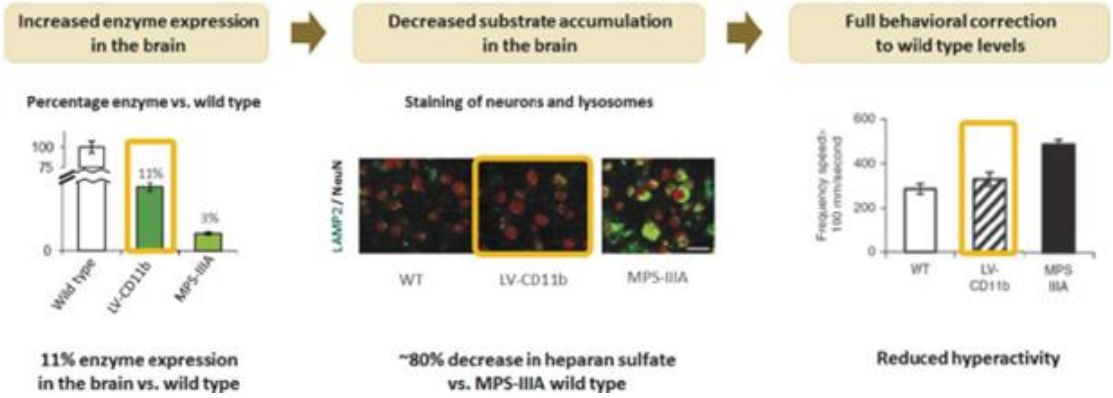
Preclinical studies

A comprehensive panel of preclinical studies has been performed by The University of Manchester, which we believe supports the use of OTL-201 in clinical trials.

In a mouse model of MPS-IIIA, engraftment of HSCs from a donor mouse modified with GFP using autologous *ex vivo* gene therapy with the selected vector for this program (a hCD11b-coSGSH lentiviral vector) was observed. Sustained gene expression of the GFP-modified HSCs was seen over a follow-up of approximately six months, which we believe supports the stability of the engraftment of modified cells.

Transplantation of gene-modified HSCs resulted in a 4.72-fold increase in enzyme activity relative to wild type enzyme levels and significantly elevated brain enzyme activity. Increased enzyme activity resulted in decreased heparan sulphate substrate accumulation in the brain and correction of behavioral abnormalities, such as hyperactivity and a reduced sense of danger, to normal levels.

The figures below illustrate the increased enzyme expression observed in the brain, the corresponding decreased substrate accumulation in the brain, and the resulting behavioural correction in a mouse model of MPS-IIIA.



Preclinical studies in a mouse model of MPS-IIIB have demonstrated correction of neurological activity, as measured by reduction in hyperactivity. Lentivirus vector optimization for OTL-202 for treatment of MPS-IIIB is ongoing.

Future applications of our autologous ex vivo gene therapy approach

We believe that our versatile autologous *ex vivo* gene therapy approach has the potential to deliver promising gene therapies to patients across a broad range of rare diseases. Although our initial focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from ADA-SCID, MLD, WAS, X-CGD and TDBT, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other rare diseases in our target franchise areas, including primary immune deficiencies, neurometabolic disorders and hemoglobinopathies, where *ex vivo* gene therapy has a comparably high probability of success.

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.

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 Annual Report 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 Annual Report 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.

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 signed a lease for a facility in Fremont, California in which we 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, including evaluation of transduction enhancers, in order 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-103, OTL-200 and OTL-300 programs and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. We plan to establish cryopreserved product formulations as the standard for all of our future gene therapy candidates.

In the cryopreservation process, a patient's gene-modified HSCs are frozen at extremely low temperatures and then stored to allow quality control testing and release to be performed before introducing the cells back into the patient. Our cryopreserved formulations are expected to have shelf-lives of months to years, enabling us to potentially distribute our products and product candidates from a few centralized manufacturing facilities to geographically dispersed treatment sites. Our ability to ultimately distribute our product candidates globally will facilitate access of the therapies to patients, and reduces the logistical burden on the patients and their families.

Intellectual property and barriers to entry

Our commercial success depends, in part, upon our ability to protect commercially important and proprietary aspects of our business, defend and enforce our intellectual property rights, preserve the confidentiality of our know-how and trade secrets, and operate without infringing misappropriating and otherwise violating valid and enforceable intellectual property rights of others. In particular, we strive to protect the proprietary aspects of our business and to develop barriers to entry that we believe are important to the development and commercialization of our gene therapies. For example, where appropriate, we develop, or acquire exclusive rights to, clinical data for Strimvelis and each of our product candidates, know-how and trade secrets associated with Strimvelis and each of our product candidates. However, we do not own any patents or patent applications that cover Strimvelis or any of our product candidates. We in-license from UCLB and UCLA one family of patent applications directed at OTL-101. We cannot guarantee that patents will issue from any of these patent applications or from any patent applications we or our licensors may file in the future, nor can we guarantee that any patents that may issue in the future from such patent applications will be commercially useful in protecting Strimvelis or our product candidates. In addition, we plan to rely on regulatory protection based on orphan drug exclusivities, data exclusivities and market exclusivities. See "—Government regulation" for additional information.

We currently rely primarily on know-how and trade secret protection for aspects of our proprietary technologies that we or our licensors believe are not amenable to or appropriate for patent protection, including, for example, clinical data and production information for Strimvelis and each of our product candidates. However, know-how and trade secrets can be difficult to protect. Although we take steps to protect our know-how, trade secrets and other proprietary information, including restricting access to our premises and our confidential information, as well as entering into agreements with our employees, consultants, advisors and potential collaborators, third parties may independently develop the same or similar know-how, trade secrets or proprietary information or may otherwise gain access to such know-how, trade secrets and other proprietary information or such know-how, trade secrets or other proprietary information may otherwise become known. Moreover, we cannot guarantee that our confidentiality agreements will provide meaningful protection or that they may not be breached and we may not have an adequate remedy for any such breach. As a result, we may be unable to meaningfully protect our know-how, trade secrets and other proprietary information.

In addition, with regard to patent protection, the scope of coverage being sought in a patent application may be reduced significantly before a patent is issued, and even after issuance the scope of coverage may be challenged. As a result, we cannot guarantee that any of our product candidates will be protectable or remain protected by enforceable patents. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient proprietary protection from competitors. Any patents that we hold may be challenged, circumvented or invalidated by third parties.

With regards to our OTL-101 product candidate, we have exclusive, worldwide, sub-licensable, licenses pursuant to the UCLB/UCLA Agreement to clinical data and to a patent family containing one pending U.S. patent application with composition of matter claims directed to the OTL-101 product candidate and its use in the treatment of ADA-SCID, and one pending counterpart European patent application. The U.S. patent application, if issued as a U.S. patent, would be expected to expire in 2036, without taking a potential patent term adjustment or extension into account. In addition, under the UCLB/UCLA Agreement, we have non-exclusive, worldwide, sub-licensable, licenses to know-how and materials relating to the OTL-101 product candidate.

With regards to Strimvelis, OTL-103, OTL-200 and OTL-300, and as discussed in detail in "—License agreements", we have exclusive, worldwide, sub-licensable licenses pursuant to the GSK Agreement and the R&D Agreement to anonymized patient-level data arising from the clinical trials of Strimvelis, OTL-103, OTL-200 and OTL-300 and know-how, including other clinical data and production information relating to Strimvelis, OTL-103, OTL-200, and OTL-300.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment, which provides additional term caused by administrative delays at the USPTO in granting a patent, or may be shortened it a patent is terminally disclaimer over another patent with an earlier expiration date.

Furthermore, in the United States, the term of a patent covering an FDA-approved drug may be eligible for a patent term extension under the Hatch-Waxman Amendments as compensation for the loss of patent term during the FDA regulatory review process. The period of extension may be up to five years beyond the expiration of the patent but cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval. Only one patent among those eligible for an extension may be extended. Similar provisions are available in Europe and in certain other jurisdictions to extend the term of a patent that covers an approved drug. In the future, if we obtain an issued U.S. patent covering one of our present or future product candidates, and if such product candidate receives FDA approval, we expect to apply for a patent term extension, if available, to extend the term of the patent covering such approved product candidate. We also expect to seek patent term extensions in any jurisdictions where they are available, however, there is no guarantee that the applicable authorities, including the FDA, will agree with our assessment of whether such an extension should be granted, and even if granted, the length of such an extension.

License agreements

GSK asset purchase and license agreement

In April 2018, we entered into the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, GSK novated to us their R&D Agreement with Telethon-OSR.

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 12,455,252 of our Series B-2 convertible preferred shares and we recorded a payable due to GSK of £4.9 million. The Series B-2 convertible preferred shares were converted to ordinary shares as part of our IPO.

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 in 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, and options on three additional earlier-stage development programs.

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, sublicensable, worldwide license under certain intellectual property rights to develop and commercialize certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD, TDBT, as well as three additional earlier-stage development programs. Our options under the R&D Agreement with respect to the three earlier-stage programs have lapsed. 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 €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). 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 under the UCLB/UCLA Agreement, and we issued to UCLB 1,224,094, and 3,441,290 of our ordinary shares in 2017 and 2016, respectively. We are also required to make certain annual administration payments to UCLB upon our receipt of VAT invoices.

Under the UCLB/UCLA Agreement, we are also obligated to pay UCL royalties ranging from low to mid-single-digit percentages on net sales of each of the product candidates subject to the UCLB/UCLA Agreement that receive marketing approval. Our royalty obligations under the UCLB/UCLA Agreement terminate in February 2041. In addition, we are required to pay to UCLB milestone payments up to an aggregate of £28.85 million upon achievement of our first, second and third marketing approvals of product candidates under the UCLB/UCLA Agreement.

Unless terminated earlier, the UCLB/UCLA Agreement will expire in February 2041. We may terminate the UCLB/UCLA Agreement in its entirety or with respect to either UCLB or UCLA for any reason upon prior written notice. Additionally, either we or UCLB may terminate the UCLB/UCLA Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time, or if the other party becomes insolvent.

Oxford BioMedica License and Development Agreement

In November 2016, we entered into a license and development agreement, or the Oxford Development Agreement, with Oxford BioMedica (UK) Limited, or Oxford BioMedica, for the development of gene therapies for ADA-SCID, MPS-IIIA and certain other diseases that we may request be included under the Oxford Development Agreement, such other diseases referred to as Subsequent Indications. The Oxford Development Agreement was amended in June 2017, May 2018, July 2018 and September 2018.

Pursuant to the Oxford Development Agreement, Oxford BioMedica granted us an exclusive, worldwide license under certain intellectual property rights for the purposes of research, development and commercialization of *ex vivo* gene therapy products for the treatment of ADA-SCID, MPS-IIIA and Subsequent Indications, except that such license is non-exclusive to the extent the treatment of a Subsequent Indication is the subject of a certain previous license granted by Oxford BioMedica. Oxford BioMedica also granted us a non-exclusive, worldwide license under certain intellectual property rights for the purposes of research, development, commercialization and manufacture of *ex vivo* gene therapy products for the treatment of certain diseases other than ADA-SCID, MPS-IIIA and Subsequent Indications. Under the Oxford Development Agreement, Oxford BioMedica is required to use commercially reasonable efforts to perform the activities set forth in a collaboration plan approved by a joint steering committee, and we are responsible for certain costs of the activities set forth in such collaboration plan.

As consideration for the licenses granted under the agreement, we issued 588,220 of our ordinary shares to Oxford BioMedica. We are also obligated to issue additional equity upon the achievement of certain milestones, pursuant to which we issued 150,826 ordinary shares upon the achievement of the first milestone in November 2017 and 150,826 ordinary shares were issued upon the achievement of further milestones in August 2018. We will be required to issue additional ordinary shares to Oxford BioMedica upon achievement of the remaining milestone under the Oxford Development Agreement. Additionally, we are obligated to pay low single-digit royalties on net sales of licensed products until January 31, 2039. The foregoing royalties are reduced by a mid-double digit percentage in the case of compassionate use of a licensed product in a country until the first commercial sale following marketing authorization in such country. We are also required to pay a set monthly fee to Oxford BioMedica in the event we use a certain Oxford BioMedica system for generating stable cell lines.

Unless terminated earlier, the Oxford Development Agreement will expire when no further payments are due to Oxford BioMedica. We may terminate the performance of the collaboration plan upon notice to Oxford BioMedica, and either party may terminate the performance of the collaboration plan or the Oxford Development Agreement if the other party commits a material breach that is not cured within a certain period of time. Either party may also terminate the Oxford Development Agreement in the event the other party becomes insolvent.

Competition

The biotechnology and pharmaceutical industries are characterized by intense and rapidly changing competition to develop new technologies and proprietary products. While we believe that our portfolio of product candidates and scientific expertise in gene therapy provides us with competitive advantages, we face potential competition from many different sources.

We face competition not only from gene therapy companies, but also from companies that are developing novel, non-gene therapy approaches or improving existing treatment approaches. Depending on how successful these efforts are, it is possible they may increase the barriers to adoption and success for our product candidates, if approved.

We are currently aware of the following competitive approaches:

- **ADA-SCID**: The current standards of care for the treatment of ADA-SCID are HSCT and chronic ERT. Adagen, marketed by Leadiant Biosciences, is the only approved ERT for ADA-SCID. We are aware that Leadiant Biosciences has filed a supplemental BLA for elapegademase, a pegylated recombinant version of Adagen, for the treatment of ADA-SCID.
- **MLD**: There is currently no effective treatment option for patients with MLD. HSCT has demonstrated limited efficacy in arresting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. We are aware that the Institut National de la Santé Et de la Recherche Médicale and Bicêtre hospital in Paris are investigating intracerebral gene therapy for MLD using an adenovirus AAV-10 vector in a clinical trial. We are also aware that Shire is investigating ERT for MLD with a biweekly intrathecal infusion. We are also aware that Shenzhen University is evaluating a lentiviral *ex vivo* gene therapy for MLD.
- **WAS**: The current standard of care for WAS is HSCT. Patients who are unable to match with a blood donor or who are otherwise ineligible for HSCT may pursue palliative care options, including intravenous immunoglobulin and antimicrobials to prevent and treat infections, topical corticosteroids to manage outbreaks of eczema, platelet transfusions to treat severe bleeds, and immunosuppressive drugs, such as rituximab, to counter autoimmune manifestations. Splenectomy may also be used to treat thrombocytopenia. These palliative approaches do not slow disease progression or address the underlying etiology of WAS. We are also aware that Généthon and Boston Children's Hospital are sponsoring clinical trials with autologous *ex vivo* lentiviral gene therapy. We do not currently have a license or an option to acquire a license from Généthon to these clinical trials in WAS and accordingly Généthon or its licensee may elect to compete against us with respect to this program. To our knowledge no other gene therapy approaches are being currently investigated in WAS.
- **X-CGD**: Management options for patients with X-CGD include prophylactic antibiotics, antifungal medications and interferon-gamma. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. We are aware that Généthon is sponsoring a clinical trial for X-CGD with an autologous *ex vivo* lentiviral gene therapy in France. We are party to an exclusive option and license agreement with Généthon, pursuant to which we have the right to exercise an option with respect to this ongoing clinical trial, which option expires in June 2019. In the event we elect not to exercise this option, Généthon or its licensee may elect to pursue a competitive program in X-CGD using any intellectual property or clinical data derived from this ongoing clinical trial.

- **TDBT:** The current standard of care for the treatment of TDBT involves chronic blood transfusions to address anemia combined with iron chelation therapy to manage the iron overload often associated with such chronic blood transfusions. HSCT is also a treatment option for some patients for whom a sufficiently well-matched donor is identified. TDBT is a highly competitive research area with several novel approaches under investigation. We are aware that bluebird bio is investigating LentiGlobin, an autologous *ex vivo* gene therapy, for treatment of TDBT and sickle cell disease. In October 2018, bluebird bio announced that the EMA had accepted its MAA for Lentiglobin for the treatment of adolescents and adults with TDBT and a non-ß0/ß0 genotype. bluebird bio has publicly announced its intention to file a BLA in the United States for Lentiglobin in the future. In addition, Memorial Sloane Kettering Cancer Center has been conducting a clinical trial utilizing a lentiviral vector. In addition, we are aware that Sangamo is investigating zinc finger nuclease-mediated gene-correction techniques in TDBT. Several other groups are developing gene editing approaches for beta-thalassemia, including CRISPR Therapeutics, EDITAS and Intellia Therapeutics. CRISPR Therapeutics' CTA for its gene editing approach for beta-thalassemia was approved in 2018. Several other non-gene therapy approaches are under investigation to improve treatment outcomes in beta-thalassemia.

Many of our potential competitors, alone or with their strategic partners, have substantially greater financial, technical and other resources than we do, such as larger research and development, clinical, marketing and manufacturing organizations. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated among a smaller number of competitors. Our commercial opportunity could be reduced or eliminated if competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than any products that we may develop. Competitors also may obtain FDA, EMA or other regulatory approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. Additionally, technologies developed by our competitors may render our potential product candidates uneconomical or obsolete, and we may not be successful in marketing our product candidates against competitors.

Government regulation

In the United States, biological products, including gene therapy products, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or FD&C Act, and the Public Health Service Act, or PHS Act, and other federal, state, local and foreign statutes and regulations. Both the FD&C Act and the PHS Act and their corresponding regulations govern, among other things, the research, development, clinical trial, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products. Each clinical trial protocol for a gene therapy product must be reviewed by the FDA, and, in some instances, the NIH, through its RAC. FDA approval must be obtained before the marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources and we may not be able to obtain the required regulatory approvals.

Within the FDA, the CBER regulates gene therapy products. The CBER works closely with the NIH and its RAC, which makes recommendations to the NIH on gene therapy issues and engages in a public discussion of scientific, safety, ethical and societal issues related to proposed and ongoing gene therapy protocols. The FDA and the NIH have published guidance documents with respect to the development and submission of gene therapy protocols. The FDA also has published guidance documents related to, among other things, gene therapy products in general, their preclinical assessment, observing subjects involved in gene therapy studies for delayed adverse events, potency testing, and chemistry, manufacturing and control information in IND for gene therapies. In July 2018, FDA issued draft guidance documents for public comment involving various aspects of gene therapy product development, review, and approval. If finalized by FDA, these guidance documents would represent FDA's current thinking on the development of gene therapy products for specific disease categories, including for rare diseases, as well as update and replace FDA's previous guidance on manufacturing issues related to gene therapy products and long-term follow-up observational studies for gene therapy products.

Ethical, social and legal concerns about gene therapy, genetic testing and genetic research could result in additional laws and regulations restricting or prohibiting the processes we may use. Federal and state legislatures, agencies, congressional committees and foreign governments have expressed interest in further regulating biotechnology. More restrictive laws and regulations or interpretations of existing laws or regulations, or claims that our products are unsafe or pose a hazard could prevent us from commercializing any products. New government requirements may be established that could delay or prevent regulatory approval of our product candidates under development. It is impossible to predict whether legislative changes will be enacted, regulations, policies or guidance changed, or interpretations by agencies or courts changed, or what the impact of such changes, if any, may be.

U.S. Biological products development process

The process required by the FDA before a biological product may be marketed in the United States generally involves the following:

- completion of nonclinical laboratory tests and animal studies according to GLPs, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an independent IRB or ethics committee at each clinical trial site before each study may be initiated;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as GCPs and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a BLA for marketing approval that includes substantive evidence of safety, purity, and potency from results of nonclinical testing and clinical trials;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities where the biological product is produced to assess compliance with CGMP to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity and, if applicable, the FDA's current good tissue practices, or CGTPs, for the use of human cellular and tissue products;
- potential FDA audit of the nonclinical study and clinical trial sites that generated the data in support of the BLA in accordance with any applicable expedited programs or designations;
- payment of user fees for FDA review of the BLA (unless a fee waiver applies); and
- FDA review and approval, or licensure, of the BLA.

Before testing any biological product candidate, including a gene therapy product, in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product biological characteristics, chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

Where a gene therapy study is conducted at, or sponsored by, institutions receiving NIH funding for recombinant DNA research, prior to the submission of an IND to the FDA, a protocol and related documentation are submitted to and the study is registered with the NIH Office of Science Policy, or OSP, pursuant to the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Compliance with the NIH Guidelines is mandatory for investigators at institutions receiving NIH funds for research involving recombinant DNA; however, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them. The NIH is responsible for convening the RAC, a federal advisory committee that discusses protocols that raise novel or particularly important scientific, safety or ethical considerations, at one of its quarterly public meetings. The OSP will notify the FDA of the RAC's decision regarding the necessity for full public review of a gene therapy protocol. RAC proceedings and reports are posted to the OSP web site and may be accessed by the public.

The clinical trial sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. Some preclinical testing may continue even after the IND is submitted. An IND is a request for authorization from the FDA to ship an unapproved, investigational product in interstate commerce and to administer it to humans, and must become effective before clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA places the clinical trial on a clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. With gene therapy protocols, if the FDA allows the IND to proceed, but the RAC decides that full public review of the protocol is warranted, the FDA will request at the completion of its IND review that sponsors delay initiation of the protocol until after completion of the RAC review process. The FDA also may impose clinical holds on a biological product candidate at any time before or during clinical trials due to, among other considerations, unreasonable or significant safety concerns, inability to assess safety concerns, lack of qualified investigators, a misleading or materially incomplete investigator brochure, study design deficiencies, interference with the conduct or completion of an a study designed to be adequate and well-controlled for the same or another investigational drug, insufficient quantities of investigational product, lack of effectiveness, or non-compliance. If the FDA imposes a clinical hold, studies may not recommence without FDA authorization and then only under terms authorized by the FDA. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues or circumstances will not arise that delay, suspend or terminate such studies.

Clinical trials involve the administration of the biological product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the study sponsor's control. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety, including stopping rules that assure a clinical trial will be stopped if certain adverse events should occur. Each protocol and any amendments to the protocol must be submitted to the FDA as part of the IND. Clinical trials must be conducted and monitored in accordance with the FDA's regulations comprising the GCP requirements, including the requirement that all research subjects provide informed consent. Further, each clinical trial and its related documentation must be reviewed and approved by an IRB at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of study participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the form and content of the informed consent that must be signed by each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Clinical research involving recombinant DNA that is subject to NIH guidelines also must be reviewed by an IBC, a local institutional committee that reviews and oversees basic and clinical research conducted at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment.

In August 2018, the NIH published a notice in the Federal Register to seek public comment on its proposal to amend the NIH Guidelines to streamline oversight for human gene transfer clinical research protocols and reduce duplicative reporting requirements while focusing the NIH Guidelines more specifically on biosafety issues associated with research involving recombinant or synthetic nucleic acid molecules. The notice included proposed amendments to eliminate RAC review and reporting requirements to NIH for human gene transfer research protocols and to modify the roles and responsibilities of investigators, institutions, IBCs, the RAC, and the NIH to be consistent with these goals.

Clinical trials typically are conducted in three sequential phases that may overlap or be combined:

- *Phase 1*. The biological product is initially introduced into healthy human subjects and tested for safety. In the case of some products for severe or life-threatening diseases, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.
- *Phase 2*. The biological product is evaluated in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance, optimal dosage and dosing schedule.
- *Phase 3*. Clinical trials are undertaken to further evaluate dosage, clinical efficacy, potency, and safety in an expanded patient population at geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the product and provide an adequate basis for approval and product labeling.

Post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up. The FDA recommends that sponsors observe subjects for potential gene therapy-related delayed adverse events for a 15-year period, including a minimum of five years of annual examinations followed by ten years of annual queries, either in person or by questionnaire, of study subjects.

Both the FDA and the EMA provide expedited pathways for the development of drug product candidates for treatment of rare diseases, particularly life threatening diseases with high unmet medical need. Such drug product candidates may be eligible to proceed to registration following a single clinical trial in a limited patient population, sometimes referred to as a Phase 1/2 trial, but which may be deemed a pivotal or registrational trial following review of the trial's design and primary endpoints by the applicable regulatory agencies. Determination of the requirements to be deemed a pivotal or registrational trial is subject to the applicable regulatory authority's scientific judgement and these requirements may differ in the U.S. and the European Union.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, efficacy, purity and potency of human gene therapy products, or that the data generated in these studies will be acceptable to the FDA to support marketing approval. The NIH has a publicly accessible database, the Genetic Modification Clinical Research Information System which includes information on gene transfer studies and serves as an electronic tool to facilitate the reporting and analysis of adverse events on these studies.

Concurrent with clinical trials, companies usually complete additional animal studies and also must develop additional information about the physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with CGMP requirements. To help reduce the risk of the introduction of adventitious agents with use of biological products, the PHS Act emphasizes the importance of manufacturing control for products whose attributes cannot be precisely defined. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, the sponsor must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the biological product candidate does not undergo unacceptable deterioration over its shelf life.

U.S. review and approval processes

After the completion of clinical trials of a biological product, FDA approval of a BLA must be obtained before commercial marketing of the biological product. The BLA must include results of product development, laboratory and animal studies, human studies, information on the manufacture and composition of the product, proposed labeling and other relevant information. The testing and approval processes require substantial time and effort and there can be no assurance that the FDA will accept the BLA for filing and, even if filed, that any approval will be granted on a timely basis, if at all.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the FDA accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. In most cases, the submission of a BLA is subject to a substantial application user fee, although the fee may be waived under certain circumstances. Under the performance goals and policies implemented by the FDA under the Prescription Drug User Fee Act, or PDUFA, for original BLAs, the FDA targets ten months from the filing date in which to complete its initial review of a standard application and respond to the applicant, and six months from the filing date for an application with priority review. The FDA does not always meet its PDUFA goal dates, and the review process is often significantly extended by FDA requests for additional information or clarification. This review typically takes twelve months from the date the BLA is submitted to the FDA because the FDA has approximately two months to make a ''filing'' decision. The review process and the PDUFA goal date may be extended by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe and potent, or effective, for its intended use, and has an acceptable purity profile, and whether the product is being manufactured in accordance with CGMP to assure and preserve the product's identity, safety, strength, quality, potency and purity. The FDA may refer applications for novel biological products or biological products that present difficult or novel questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. During the biological product approval process, the FDA also will determine whether a REM is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA typically will inspect the facilities at which the product is manufactured. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with CGMP requirements and adequate to assure consistent production of the product within required specifications. For a gene therapy product, the FDA also will not approve the product if the manufacturer is not in compliance with the CGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue-based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the CGTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through appropriate screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure that the clinical trials were conducted in compliance with IND study requirements and GCP requirements. To assure CGMP, CGTP and GCP compliance, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

Under the Pediatric Research Equity Act, or PREA, a BLA or supplement to a BLA for a novel product (e.g., new active ingredient, new indication, etc.) must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any biological product for an indication for which orphan designation has been granted.

Notwithstanding the submission of relevant data and information, the FDA may ultimately decide that the BLA does not satisfy its regulatory criteria for approval and deny approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data. If the FDA decides not to approve the BLA in its present form, the FDA will issue a complete response letter that usually describes all of the specific deficiencies in the BLA identified by the FDA. The deficiencies identified may be minor, for example, requiring labeling changes, or major, for example, requiring additional clinical trials. Additionally, the complete response letter may include recommended actions that the applicant might take to place the application in a condition for approval. If a complete response letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, including to subpopulations of patients, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings precautions or interactions be included in the product labeling. The FDA may impose restrictions and conditions on product distribution, prescribing, or dispensing in the form of a REMS, or otherwise limit the scope of any approval. In addition, the FDA may require post marketing clinical trials, sometimes referred to as Phase 4 clinical trials, designed to further assess a biological product's safety and effectiveness, and testing and surveillance programs to monitor the safety of approved products that have been commercialized.

Orphan drug designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting a BLA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

Orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the European Union has similar, but not identical, benefits.

Expedited development and review programs

The FDA has various programs, including Fast Track designation, breakthrough therapy designation, accelerated approval and priority review, that are intended to expedite or simplify the process for the development and FDA review of drugs and biologics that are intended for the treatment of serious or life-threatening diseases or conditions. These programs do not change the standards for approval but may help expedite the development or approval process. To be eligible for fast track designation, new drugs and biological products must be intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. One benefit of fast track designation, for example, is that the FDA may consider for review sections of the marketing application for a product that has received Fast Track designation on a rolling basis before the complete application is submitted.

Under the FDA's breakthrough therapy program, products intended to treat a serious or life-threatening disease or condition may be eligible for the benefits of the Fast Track program when preliminary clinical evidence demonstrates that such product may have substantial improvement on one or more clinically significant endpoints over existing therapies. Additionally, the FDA will seek to ensure the sponsor of a breakthrough therapy product receives timely advice and interactive communications to help the sponsor design and conduct a development program as efficiently as possible.

Any product is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Under priority review, the FDA's goal is to review an application in six months once it is filed, compared to ten months for a standard review.

Additionally, a product may be eligible for accelerated approval. Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on an intermediate clinical endpoint other than survival or irreversible morbidity. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

RMAT designation

As part of the 21st Century Cures Act, enacted in December 2016, Congress amended the FD&C Act to facilitate an efficient development program for, and expedite review of RMAT, which include cell and gene therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products. RMAT do not include those HCT/Ps regulated solely under section 361 of the PHS Act and 21 CFR Part 1271. This program is intended to facilitate efficient development and expedite review of regenerative medicine therapies, which are intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition and qualify for RMAT designation. A drug sponsor may request that FDA designate a drug as a RMAT concurrently with or at any time after submission of an IND. FDA has 60 calendar days to determine whether the drug meets the criteria, including whether there is preliminary clinical evidence indicating that the drug has the potential to address unmet medical needs for a serious or life-threatening disease or condition. A BLA for a regenerative medicine therapy that has received RMAT designation may be eligible for priority review or accelerated approval through use of surrogate or intermediate endpoints reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of sites. Benefits of RMAT designation also include early interactions with FDA to discuss any potential surrogate or intermediate endpoint to be used to support accelerated approval. A regenerative medicine therapy with RMAT designation that is granted accelerated approval and is subject to post-approval requirements may fulfill such requirements through the submission of clinical evidence from clinical trials, patient registries, or other sources of real world evidence, such as electronic health records; the collection of larger confirmatory data sets; or post-approval monitoring of all patients treated with such therapy prior to its approval. Like some of FDA's other expedited development programs, RMAT designation does not change the standards for approval but may help expedite the development or approval process.

Post-approval requirements

Maintaining substantial compliance with applicable federal, state, and local statutes and regulations requires the expenditure of substantial time and financial resources. Rigorous and extensive FDA regulation of biological products continues after approval, particularly with respect to CGMP. We currently rely, and may continue to rely, on third parties for the production of clinical and commercial quantities of any products that we may commercialize. Manufacturers of our products are required to comply with applicable requirements in the CGMP regulations, including quality control and quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products, include reporting of CGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting updated safety and efficacy information, and complying with electronic record and signature requirements. After a BLA is approved, the product also may be subject to official lot release. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer submits samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA also may perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer. In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency, and effectiveness of biological products.

We also must comply with the FDA's advertising and promotion requirements, such as those related to direct-to-consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product's approved labeling (known as "off-label use"), industry-sponsored scientific and educational activities, and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors or other stakeholders, debarment, restitution, disgorgement of profits, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Biological product manufacturers and other entities involved in the manufacture and distribution of approved biological products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with CGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain CGMP compliance. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including withdrawal of the product from the market. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further FDA review and approval.

U.S. Patent term restoration and marketing exclusivity

Depending upon the timing, duration and specifics of the FDA approval of the use of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of a BLA plus the time between the submission date of a BLA and the approval of that application. Only one patent applicable to an approved biological product is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. In addition, a patent can only be extended once and only for a single product. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we may intend to apply for restoration of patent term for one of our patents, if and as applicable, to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant BLA.

A biological product can obtain pediatric market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

The ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009 which created an abbreviated approval pathway for biological products shown to be similar to, or interchangeable with, an FDA-licensed reference biological product. This amendment to the PHS Act attempts to minimize duplicative testing. Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency, can be shown through analytical studies, animal studies, and a clinical trial or trials. Interchangeability requires that a product is biosimilar to the reference product and the product must demonstrate that it can be expected to produce the same clinical results as the reference product and, for products administered multiple times, the biologic and the reference biologic may be switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biologic. However, complexities associated with the larger, and often more complex, structure of biological products, as well as the process by which such products are manufactured, pose significant hurdles to implementation that are still being worked out by the FDA.

A reference biological product is granted four and 12 year exclusivity periods from the time of first licensure of the product. FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product, and FDA will not approve an application for a biosimilar or interchangeable product based on the reference biological product until twelve years after the date of first licensure of the reference product. "First licensure" typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest, or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity, or potency. Therefore, one must determine whether a new product includes a modification to the structure of a previously licensed product that results in a change in safety, purity, or potency to assess whether the licensure of the new product is a first licensure that triggers its own period of exclusivity. Whether a subsequent application, if approved, warrants exclusivity as the "first licensure" of a biological product is determined on a case-by-case basis with data submitted by the sponsor.

Additional regulation

In addition to the foregoing, state and federal laws regarding environmental protection and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous substances, we could be liable for damages and governmental fines. We believe that we are in material compliance with applicable environmental laws and that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations.

U.S. Foreign Corrupt Practices act

The U.S. Foreign Corrupt Practices Act, to which we are subject, prohibits corporations and individuals from engaging in certain activities to obtain or retain business or to influence a person working in an official capacity. It is illegal to pay, offer to pay or authorize the payment of anything of value to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business or to otherwise influence a person working in an official capacity.

Government regulation outside of the United States

In addition to regulations in the United States, we are subject to a variety of regulations in other jurisdictions governing, among other things, research and development, clinical trials, testing, manufacturing, safety, efficacy, labeling, packaging, storage, record keeping, distribution, reporting, advertising and other promotional practices involving biological products as well as authorization and approval of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries.

Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical trial application much like the IND prior to the commencement of human clinical trials. In the European Union, for example, a CTA must be submitted for each clinical trial to each country’s national health authority and an independent ethics committee, much like the FDA and an IRB, respectively. Once the CTA is approved in accordance with a country’s requirements, the corresponding clinical trial may proceed.

The requirements and process governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

Regulation in the European Union

In the European Union, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the European Union and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products, which are cells or tissues that have undergone substantial manipulation and that are administered to human beings in order to regenerate, repair or replace a human tissue. We anticipate that our gene therapy development products would be regulated as ATMPs in the European Union.

To obtain regulatory approval of an investigational product under European Union regulatory systems, we must submit an MAA. The application used to submit the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, region-specific document requirements. The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator’s data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator’s data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union’s regulatory authorities to be an innovative medicinal product, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five (5) in ten thousand (10,000) persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical trials must be conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension of clinical trials, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Pediatric development

In the European Union, companies developing a new medicinal product must agree upon a Pediatric Investigation Plan, or PIP, with the EMA, and must conduct pediatric clinical trials in accordance with that PIP, unless a waiver applies, (e.g., because the relevant disease or condition occurs only in adults). The marketing authorization application for the product must include the results of pediatric clinical trials conducted in accordance with the PIP, unless a waiver applies, or a deferral has been granted, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization on the basis of the pediatric clinical trials conducted in accordance with the PIP are eligible for a six month extension of the protection under a supplementary protection certificate (if any is in effect at the time of approval) or, in the case of orphan medicinal products, a two year extension of the orphan market exclusivity. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

Post-approval controls

The holder of a marketing authorization must establish and maintain a pharmacovigilance system and appoint an individual qualified person for pharmacovigilance, who is responsible for oversight of that system. Key obligations include expedited reporting of suspected serious adverse reactions and submission of periodic safety update reports, or PSURs.

All new MAAs must include a risk management plan, or RMP, describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the marketing authorization. Such risk-minimization measures or post-authorization obligations may include additional safety monitoring, more frequent submission of PSURs, or the conduct of additional clinical trials or post-authorization safety studies. RMPs and PSURs are routinely available to third parties requesting access, subject to limited redactions.

All advertising and promotional activities for the product must be consistent with the approved SmPC and therefore all off-label promotion is prohibited. Direct-to-consumer advertising of prescription medicines is also prohibited in the European Union. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Other healthcare laws and compliance requirements

In the United States, our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to, the Centers for Medicare and Medicaid Services, or CMS, other divisions of the U.S. Department of Health and Human Services, or HHS (such as the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration), the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. For example, our clinical research, sales, marketing and scientific/educational grant programs may have to comply with the anti-fraud and abuse provisions of the Social Security Act, the false claims laws, the privacy and security provisions of the Health Insurance Portability and Accountability Act, or HIPAA, and similar state laws, each as amended, as applicable:

- the federal Anti-Kickback Statute, which prohibits, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe, or rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce, or in return for, either the referral of an individual, or the purchase, lease, order, arrangement or recommendation of any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs; a person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act or federal civil money penalties statute;
- the federal civil and criminal false claims laws and civil monetary penalty laws, including the False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, false or fraudulent claims for payment to, or approval by Medicare, Medicaid, or other federal healthcare programs, knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or an obligation to pay or transmit money to the federal government, or knowingly concealing or knowingly and improperly avoiding or decreasing or concealing an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payers if they are deemed to “cause” the submission of false or fraudulent claims. The False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- 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.

Some of the provisions of the ACA have yet to be implemented, and there have been legal and political challenges to certain aspects of the ACA. Since January 2017, President Trump has signed two executive orders and other directives designed to delay, circumvent, or loosen certain requirements mandated by the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, 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." 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 excise tax on non-exempt medical devices. The Bipartisan Budget Act of 2018, or the BBA, among other things, amends the ACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole". In July 2018, CMS announced that it is suspending further collections and payments to and from certain ACA qualified health plans and health insurance issuers under the Affordable Care Act risk adjustment program pending the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or the Texas District Court Judge, ruled that the individual mandate is a critical and inserverable feature of the ACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the ACA are invalid as well. The Texas District Court Judge, as well as the Trump Administration and CMS, have stated that the ruling will have no immediate effect, and on December 30, 2018 the Texas District Court Judge issued an order staying the judgment pending appeal. It is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA.

Other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction of at least $1.2 trillion for fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect beginning on April 1, 2013 and, due to legislation amendments to the statute, including the BBA, will stay 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 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.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2019 contains further drug price control measures that could be enacted during the 2019 budget process or in other future legislation, including, for example, measures to permit Medicare Part D plans to negotiate the price of certain drugs under Medicare Part B, to allow some states to negotiate drug prices under Medicaid, and to eliminate cost sharing for generic drugs for low-income patients. Further, the Trump administration released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in September 2018, CMS announced that it will allow Medicare Advantage Plans the option to use step therapy for Part B drugs beginning January 1, 2019, and in October 2018, CMS proposed a new rule that would require direct-to-consumer television advertisements of prescription drugs and biological products, for which payment is available through or under Medicare or Medicaid, to include in the advertisement the Wholesale Acquisition Cost, or list price, of that drug or biological product. While a number of these and other proposed measures will require authorization through additional legislation to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. Individual states in the United States have also increasingly passed legislation and implemented 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.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to request access to certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

Coverage and reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any gene therapies for which we obtain regulatory approval. In the United States and markets in other countries, sales of any gene therapies for which we receive regulatory approval for commercial sale will depend, in part, on the availability of coverage and reimbursement from payors. Payors include government authorities, managed care providers, private health insurers and other organizations. The process for determining whether a payer will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payer will pay for the product. Payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. A decision by a payor not to cover our gene therapies could reduce physician utilization of our products once approved and have a material adverse effect on our sales, results of operations and financial condition. Moreover, a payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third-party reimbursement may not be available to enable us to maintain price levels sufficient to realize an appropriate return on our investment in product development.

In addition, coverage and reimbursement for products can differ significantly from payer to payer. One payor's decision to cover a particular medical product or service does not ensure that other payers will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate.

As a result, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payer separately and will be a time-consuming process.

Payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. In order to obtain and maintain coverage and reimbursement for any product, we may need to conduct expensive clinical trials in order to demonstrate the medical necessity and cost-effectiveness of such product, in addition to the costs required to obtain regulatory approvals. If payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the European Union, pricing and reimbursement schemes vary widely from country to country. Some countries provide that products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost-effectiveness of a particular therapy to currently available therapies or so-called health technology assessments, in order to obtain reimbursement or pricing approval. Other countries may allow companies to fix their own prices for products, but monitor and control product volumes and issue guidance to physicians to limit prescriptions. Efforts to control prices and utilization of pharmaceutical products and medical devices will likely continue as countries attempt to manage healthcare expenditures.

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.

C. Organizational structure.

The following is a list of our subsidiaries:

Name	Country of Registration	Activity	% Holding
Orchard Therapeutics (Europe) Limited	England and Wales	Research and Development	100%
Orchard Therapeutics North America	United States	Research and Development	100%
Orchard Therapeutics (Netherlands) B.V.	Netherlands	Research and Development	100%

D. Property, plants and equipment.

Facilities

Our principal office is located at 108 Cannon Street, London EC4N 6EU, United Kingdom. We lease approximately 14,000 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 and 9,117 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.

On December 11, 2018, we entered into an agreement to lease approximately 152,995 square feet of manufacturing and office space in Fremont, California to support our manufacturing expansion. This lease extends through May 2030. We expect to spend approximately $84.5 million to fund the design, initial construction, and operation of this facility, including the necessary laboratory and manufacturing equipment, to support our long-term capacity needs for our product pipeline.

We believe that suitable additional or substitute space will be available as needed to accommodate any future expansion of our operations

Item 4A. Unresolved Staff Comments

There are no written comments from the staff of the U.S. Securities and Exchange Commission which remain unresolved before the end of the fiscal year to which this Annual Report relates.

Item 5. Operating and Financial Review and Prospects

You should read the following discussion and analysis of our financial condition and results of operations together with Item 3.A. "Selected consolidated financial data" and our consolidated financial statements and the related notes appearing elsewhere in this Annual Report. Some of information contained in this discussion and analysis or set forth elsewhere in this Annual Report, 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 Item 3.D. "Risk factors" section of this Annual Report, 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 "Cautionary Statement Regarding Forward-Looking Statements."

We have historically conducted our business through Orchard Therapeutics (Europe) Limited (formerly Orchard Therapeutics Limited) and our U.S. subsidiary. Following the completion of our initial public offering in November 2018, our consolidated financial statements present the consolidated results and operations of Orchard Therapeutics plc.

A. Operating results.

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.

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 and ADSs. Through December 31, 2018, we had received gross proceeds of $283.4 million from sales of our convertible preferred shares, and $205.5 million from sales of ADSs in our initial public offering.

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 $230.5 million for the years ended December 31, 2016, 2017, and 2018, respectively. As of December 31, 2018, we had an accumulated deficit of $290.2 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.

Components of our results of operations

Revenue

Since inception through December 31, 2018, we have generated $2.1 million in net 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.

During the year ended December 31, 2018, we made the first sales of Strimvelis since acquisition under the GSK Agreement and recognized $2.1 million in net product sales. Strimvelis is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. Strimvelis sales are currently under a buy-and-bill model where the treatment center purchases and pays for the product and submits a claim to the payer. We evaluated the variable consideration under Accounting Standards Codification (ASC) 606, Revenue from Contracts with Customers, and there is currently no variable consideration included in the transaction price for Strimvelis. We expect that net product sales of Strimvelis will fluctuate quarter over quarter, in particular as we continue to build and promote access. Net product sales for the year ended December 31, 2018 may not be representative of our sales for any future period.

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 have received under this agreement was $10.4 million, which may have been received during the period from January 2017 to December 2021. Through June 30, 2018, we received and recognized $7.3 million from this agreement. In July 2018, a transfer of the sponsorship took place and we became the awardee under the program funded by CIRM, and we were awarded a continuation of the ADA-SCID research award, which superseded the previous award. The total reimbursement we may receive under this award is $8.5 million, of which $5.5 million may be reimbursed to UCLA. Under the terms of the CIRM grants, we are obligated to pay royalties and licensing fees based on a low single digit royalty percentage on net sales of CIRM-funded product candidates or CIRM-funded technology. We have the option to decline any and all amounts awarded by CIRM. As an alternative to revenue sharing, we have the option to convert the award to a loan. No such election has been made as of the date of this Annual Report. These reimbursements are recognized as a reduction in research and development expense to the extent we have earned them 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 or amended.

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, for the year ended December 31, 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 9 to our consolidated financial statements in this Annual Report for additional details of the GSK Agreement and its accounting.

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

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

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

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

Selling, general and administrative expenses

Selling, general and administrative expenses consist primarily of salaries and other related costs, including share-based compensation, for personnel in our executive, finance, commercial, corporate and business development, and administrative functions. Selling, 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 selling, general and administrative expenses will increase in the future as we increase our selling, 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 compliance with our obligations as 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 for the periods ended December 31, 2018 and December 31, 2017 were $1.1 million and nil, respectively.

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 the 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 have not reflected it 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 out 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, 2017 and 2018. The Company will assess whether it is possible to qualify under the more favorable SME regime for future accounting periods, but this may be affected as a result of becoming a United States public company.

Unsurrendered U.K. losses may be carried forward indefinitely to be offset against future taxable profits, subject to numerous utilization criteria and restrictions. The amount that can be offset each year is limited to £5.0 million plus an incremental 50% of U.K. taxable profits. After accounting for tax credits receivable, we had accumulated tax losses for carry forward in the United Kingdom of $155.2 million as of December 31, 2018.

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 in the United Kingdom. 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, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		
	2018	2017	Change
	(in thousands)		
Product sales, net	$ 2,076	$ —	$ 2,076
Cost and operating expenses:			
Cost of product sales	422	—	422
Research and development	205,319	32,527	172,792
Selling, general and administrative	31,366	5,985	25,381
Total operating expenses	237,107	38,512	198,595
Loss from operations	(235,031)	(38,512)	(196,519)
Other income (expense):			
Interest income	1,116	—	1,116
Other income (expense), net	4,390	(1,179)	5,569
Total other income (expense)	5,506	(1,179)	6,685
Net loss before income tax	(229,525)	(39,691)	(189,834)
Income tax expense	(970)	(53)	(917)
Net loss attributable to ordinary shareholders	$ (230,495)	$ (39,744)	$ (190,751)

Research and development expenses

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

	Year Ended December 31,		
	2018	2017	Change
	(in thousands)		
Direct research and development expenses by program:			
OTL-200 for MLD.	$ 75,422	$ —	$ 75,422
OTL-103 for WAS.	66,728	—	66,728
OTL-101 for ADA-SCID	18,540	13,181	5,359
OTL-102 for X-CGD	2,929	1,303	1,626
OTL-201 for MPS-IIIA	4,329	3,158	1,171
Other programs	9,537	4,938	4,599
Research and discovery and unallocated costs			
Personnel related (including share-based compensation)	18,553	6,770	11,783
Facility and other	9,281	3,177	6,104
Total research and development expenses	$ 205,319	$ 32,527	$ 172,792

In April 2018, GSK transferred OTL-200, OTL-103 and OTL-102 to us resulting in increased direct research and development expenses of $75.4 million, relating to OTL-200, and $66.7 million, relating to OTL-103, and $1.6 million, relating to OTL-102 in the year ended December 31, 2018.

The increase of $75.4 million, relating to OTL-200, consists of $69.3 million of in-process research and development charges related to the GSK transaction along with $3.7 million of clinical trial costs and $2.0 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 Company also incurred $5.0 million in consulting expense generally attributable to our transition services agreement with GSK. These amounts were decreased by $4.6 million in offsets to research and development expenses associated with amortization of the Strimvelis loss provision and the UK research and development tax credit.

The increase of $66.7 million, relating to OTL-103, consists of $64.3 million of in-process research and development charges related to the GSK transaction along with $2.5 million of clinical trial costs and $3.0 million of costs to prepare our viral vector and cell manufacturing processes for patients enrolled in both fresh and cryopreserved cell formulation clinical trials. These amounts were decreased by $3.8 million in offsets to research and development expenses associated with amortization of the Strimvelis loss provision and the U.K. research and development tax credit.

Direct research and development expenses relating to OTL-101 increased by $5.4 million in the year ended December 31, 2018, primarily due to 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, increased clinical consulting and other costs of $2.0 million to prepare and activate clinical trial sites. These amounts were decreased by $6.1 million in offsets to research and development expenses associated with the U.K. research and development tax credit and our research grants with CIRM.

Direct research and development expenses relating to OTL-102 increased by $1.6 million in the year ended December 31, 2018, primarily due to increases in manufacturing costs of $2.2 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 $0.7 million to prepare and activate clinical trial sites. This is offset by a decrease of $1.3 million in costs related to in-licensing the technology relevant to the program, which were a one-time expense in 2017.

Direct research and development expenses relating to OTL-201 increased by $1.2 million in the year ended December 31, 2018. The increase primarily relates to an increase of $1.1 million in costs to prepare and activate clinical trials, and $0.7 million in milestone payments. This is offset by a decrease in pre-clinical costs of $0.8 million.

Direct research and development expenses for other programs increased by $4.6 million in the year ended December 31, 2018. This is primarily due to our acquisition of Strimvelis and OTL-300 in the GSK transaction. In the year ended December 31, 2018 we spent $5.1 million in research and development costs to maintain Strimvelis, including $1.9 million in manufacturing-related costs, $1.9 million for ongoing trial-related costs, and $1.8 million for consulting expense generally attributable to our transitional services agreement with GSK. In the year ended December 31, 2018, we spent $2.2 million on OTL-300, which consists of $2.0 million in clinical trial costs and $0.3 million in manufacturing costs. Further, in July 2018 we paid a $1.8 million milestone associated with our MPS-I clinical study. These amounts were offset by decreases in spending on other pre-clinical programs of $4.9 million.

The increase of $17.9 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 increased by $11.8 million in the year ended December 31, 2018. Personnel-related costs for each of the years ended December 31, 2018 and 2017 included share-based compensation expense of $2.7 million and $0.6 million, respectively. Facility and other costs increased primarily due to the lease of new laboratory and office space and the increased costs of supporting the increased headcount in our research and development functions and their research efforts.

Selling, general and administrative expenses

Selling, general and administrative expenses were $31.4 million for the year ended December 31, 2018, compared to $6.0 million for the year ended December 31, 2017. The increase of $25.9 million was primarily due to increased personnel-related costs of $10.9 million from an increased headcount in our selling, general and administrative function. Share-based compensation expense of $4.0 million and $0.4 million is included in selling, general and administrative expense for the year ended December 31, 2018 and 2017, respectively. Professional and consulting fees increased by $7.8 million in 2018 as a result of an increase in accounting, audit, legal, recruitment, and information technology fees as well as costs associated with ongoing business activities. Facility and other costs increased $7.2 million in 2018, primarily due to the leases of new office space and increased costs of supporting the expansion of our business. Additionally, included in the $31.4 million in selling, general and administrative expenses is $8.5 million in expenses associated with maintaining commercial availability of Strimvelis, and costs associated with potential future commercialization of our product candidates, if approved. There were no such costs in 2017.

Other income (expense), net

Other income (expense), net for the years ended December 31, 2018 and 2017 was income of $5.5 million and expense of $1.2 million, respectively. During the year ended December 31, 2018, we had realized and unrealized gains on foreign currency of $4.4 million for the year ended December 31, 2018, compared to realized and unrealized foreign currency loss of $1.2 million for the year ended December 31, 2017, primarily due to the strength of the U.S. dollar relative to the British pound as compared to 2017. Additionally, we had interest income of $1.1 million and nil for the years ended December 31, 2018 and 2017, respectively.

Comparison of the years ended December 31, 2017 and 2016

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

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

Research and development expenses

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

	Year ended December 31		
	2017	2016	Change
	(in thousands)		
Direct research and development expenses by program:			
OTL-101 for ADA-SCID	$ 13,181	$ 7,468	5,713
OTL-102 for X-CGD	1,303	—	1,303
OTL-201 for MPS-IIIA	3,158	3,565	(407)
Other programs	4,938	1,548	3,390
Research and discovery and unallocated costs			
Personnel related (including share-based compensation)	6,770	1,892	4,878
Facility and other	3,177	1,733	1,444
Total research and development expenses	$ 32,527	$ 16,206	$ 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 349,770 ordinary shares to the licensor.

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

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

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

General and administrative expenses

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

Other income (expense), net

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

B. Liquidity and capital resources.

From our inception through December 31, 2018, we have generated only $2.1 million from product sales and incurred significant operating losses and negative cash flows from our operations. We currently have only one commercial product, Strimvelis, which we acquired from GSK in April 2018 and our product candidates are in various phases of preclinical and clinical development. We do not expect to generate significant revenue from sales of any products for several years, if at all. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our initial public offering, proceeds from the sale of convertible preferred shares, reimbursements from our research agreement with UCLA and, following transfer of the ADA-SCID research program sponsorship from UCLA to us in July 2018, a grant from CIRM.

Through December 31, 2018, we had received net proceeds of $283.4 million from sales of convertible preferred shares, net proceeds of $205.5 million from the sale of ADSs in our initial public offering, and reimbursement of $7.9 million from our agreement with the California Institute of Regenerative Medicine, which was formerly a subcontract agreement with UCLA. As of December 31, 2018, we had cash of $335.8 million.

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,		
	2018	2017	2016
	(in thousands)		
Net cash used in operating activities	$ (97,536)	$ (32,487)	$ (14,566)
Net cash used in investing activities	(4,032)	(1,559)	(190)
Net cash provided by financing activities	354,864	115,696	18,034
Effect of exchange rate changes on cash	(3,471)	4,709	(751)
Net increase in cash	$ 249,825	$ 86,359	$ 2,527

Operating activities

During the year ended December 31, 2018, operating activities used $97.5 million of cash, primarily resulting from our net loss of $230.5 million, off-set by net cash provided by changes in our operating assets and liabilities of $36.5 million and net non-cash charges and credits of $96.5 million, which included $93.4 million for the issuance of our preferred shares as non-cash in-license fees under the GSK Agreement, $6.8 million in non-cash share-based compensation, $1.4 million in non-cash milestone expense, and $1.2 million in depreciation expense. These amounts were offset by a $6.3 million reduction in the Strimvelis loss provision. Net cash provided by changes in our operating assets and liabilities for the year ended December 31, 2018 is primarily due to the impact of a $10.1 million increase in our research and development tax credit receivable and a $6.8 million increase in receivables, prepaid expenses and other assets, offset by a $31.7 million increase in accrued expenses and other current liabilities, a $6.9 million increase in other long-term liabilities, and a $14.8 million increase in accounts payable. Included within operating activities was a cash payment of $14.2 million for the GSK upfront license fee.

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.

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.

The change in net cash used in operating activities from 2017 to 2018 is the result of our increased net loss, generally due to growth in our business and the advancement of our development programs, as described in “—Results of operations.”

Investing activities

During the years ended December 31, 2018, 2017, and 2016, we used $4.0 million, $1.6 million, and $0.2 million, respectively, of cash in investing activities for purchases of property and equipment.

Financing activities

During the year ended December 31, 2018, net cash provided by financing activities was $354.9 million, consisting of $2.3 million of net proceeds from subsequent closing of our Series B convertible preferred shares in January 2018, $147.1 million of net proceeds from the sale of our Series C convertible preferred shares in August 2018, and $205.5 million of net proceeds from the sale of our ADSs in our initial public offering in November 2018.

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.

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.

Funding requirements

We expect our expenses and capital expenditures 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
- comply with our obligations as 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 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.

Critical Accounting Policies 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 in this Annual Report, 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.

Valuation of 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 recognize 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 in this Annual Report, 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.

The fair value of each share option is estimated on the date of grant using the Black-Scholes option pricing model. Until the completion of our initial public offering in November 2018, we had been a private company and lacked 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.

As there has historically 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. Following our completed initial public offering, our share option grants are issued at the fair market value of our ADSs at the date the grant is approved by the Board.

We estimate the fair value of our performance-based restricted stock unit ("RSUs") awards or components of RSU awards whose vesting is contingent upon market conditions, such as volume weighted-average price ("VWAP"), using the Monte-Carlo simulation model. The fair value of RSUs or components of RSU awards where vesting is contingent upon market conditions is amortized based upon the estimated derived service period.

C. Research and development, patents and licenses, etc.

Full details of our research and development activities and expenditures are given in "Item 4.B. Information on the Company – Business overview" and "Item 5.A. Operating results" within this Annual Report.

D. Trend information.

Other than as disclosed elsewhere in this Annual Report, we are not aware of any trends, uncertainties, demands, commitments or events for the period from January 1, 2018 to December 31, 2018 that are reasonably likely to have a material adverse effect on our net revenues, income, profitability, liquidity or capital resources, or that caused the disclosed financial information to be not necessarily indicative of future operating results or financial conditions. For a discussion of trends, see "Item 5.A. Operating Results" and "Item 5.B. Liquidity and Capital Resources" within this Annual Report.

E. 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.

F. Tabular disclosure of contractual obligations.

The following table summarizes our contractual obligations as of December 31, 2018 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)	$ 10,146	$ 5,586	$ 4,560	$ —	$ —
Operating lease commitments(2)	$ 39,499	$ 3,303	$ 9,045	$ 6,765	$ 20,386
Total	$ 49,645	$ 8,889	$ 13,605	$ 6,765	$ 20,386

(1) Amounts reflect commitments for costs associated with our external CMOs, which we engaged to manufacture clinical trial materials. Our manufacturing commitment included non-cancelable minimum quantities to be purchased as of December 31, 2018.

(2) Amounts reflect minimum payments due for our office and laboratory space leases. We have two office lease in London, U.K. under operating leases that expire in January 2023. We lease laboratory space in Foster City, California and Menlo Park, California under operating leases that expire between June 2020 and October 2021. We lease manufacturing and office space in Fremont, California under an operating lease that expires in May 2030. We lease office space in Boston, Massachusetts under an operating lease that expires in September 2022.

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 office space in London, United Kingdom, with a term through January 2023. The annual rent commitment is approximately $0.8 million. In November 2017 we leased office and laboratory space in Menlo Park, California with a term through December 2020. The annual rent commitment is approximately $0.8 million. In October 2016 we leased laboratory space in Foster City, California with a term through October 2021. The annual rent commitment is approximately $0.2 million. In March 2018, we leased office space in Boston, Massachusetts, with a term through September 2022. The annual rent commitment is approximately $0.3 million. In December 2018, we leased office and manufacturing space in Fremont, California, with a term through May 2030. The annual rent commitment is approximately $2.8 million. In December 2018, we leased additional office space in London, United Kingdom, with a term through January 2023. The annual rent commitment is approximately $0.1 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. We may pay up to an aggregate of £90.0 million in 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). 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.

G. Safe harbor.

This Annual Report on Form 20-F contains forward-looking statements within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act and as defined in the Private Securities Litigation Reform Act of 1995. See the section titled “Cautionary Statement Regarding Forward-Looking Statements” at the beginning of this Annual Report.

Item 6. Directors, Senior Management and Employees

A. Directors and senior management.

The following table sets forth the name, age and position our executive officers and directors as of December 31, 2018.

Name	Age	Position(s)
Executive Officers:		
Mark Rothera	57	President, Chief Executive Officer and Director
Frank E. Thomas	49	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
Charles A. Rowland, Jr.	60	Director
Hong Fang Song	53	Director
Alicia Secor	56	Director

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. Since January 2019, Dr. Beck also serves on the board of directors of Alliance for Regenerative Medicine, an international multi-stakeholder advocacy organization. Dr. Beck holds a B.A. in Chemistry from Lewis and Clark College and a Ph.D. in Biochemistry and Molecular Biology from Oregon Health and Science University. We believe Dr. Beck is qualified to serve on our board because of her executive experience in our industry.

Marc Dunoyer has been a member of our board of directors since May 2018. Since November 2013, Mr. Dunoyer has served as the chief financial officer at AstraZeneca plc, a publicly traded pharmaceutical company. At AstraZeneca, Mr. Dunoyer also held the role of Executive Vice President, Global Portfolio & Product Strategy from June 2013 to October 2013. Additionally, Mr. Dunoyer serves on the board of directors of AstraZeneca. Prior to joining AstraZeneca, from February 2010 to March 2013, Mr. Dunoyer served as the foundational Global Head of the Rare Diseases Unit at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Mr. Dunoyer also served on the company's corporate executive team and previously held the position of President for Asia-Pacific and Japan. Mr. Dunoyer has previously held international positions in operations and general management at Hoechst Marion Roussel, a wholly owned subsidiary of Sanofi S.A., a publicly traded pharmaceutical company, and holds an M.B.A. degree from the Hautes Etudes Commerciales and a Bachelor of Law degree from Paris University. We believe Mr. Dunoyer is qualified to serve on our board because of his executive experience in our industry.

Jon Ellis, Ph.D. has been a member of our board of directors since July 2018. Since January 2016, Dr. Ellis has served as the Vice President and Head, Science & Technology Licensing Pharmaceuticals R&D at GlaxoSmithKline plc, a publicly traded pharmaceutical company. At GSK, Dr. Ellis has also held the roles of Vice President & Head of Platforms BD & Academic, Vice President & Head of Platforms BD, Vice President & Head of Biopharmaceuticals BD, as well as the Head of Antibody Engineering and Biopharm Licensing. Prior to joining GSK in 2001, Dr. Ellis worked as a group leader at GlaxoWellcome plc, a former publicly traded pharmaceutical company, from November 1995 to January 2001. Prior to joining GlaxoWellcome in 1995, Dr. Ellis was a Senior Molecular Biologist at Wellcome Foundation Ltd, a former publicly traded pharmaceutical company, from November 1993 to November 1995. Prior to joining Wellcome Foundation in 1993, Dr. Ellis was a staff scientist at Quantum Biosystems Ltd from October 1992 to November 1993. Dr. Ellis holds a B.A. and M.A. from Magdalene College, University of Cambridge, a Ph.D. from the University of Cambridge, and an M.B.A. from Henley Management College. We believe Dr. Ellis is qualified to serve on our board because of his extensive experience in our industry.

Charles A. Rowland, Jr. has been a member of our board of directors since July 2018. From April 2016 to February 2017, Mr. Rowland served as President and Chief Executive Officer of Aurinia Pharmaceuticals Inc., and as a member of the board of directors of Aurinia from July 2014 to February 2017. Mr. Rowland previously served as Vice President and Chief Financial Officer of ViroPharma Incorporated, an international biopharmaceutical company, from October 2008 until it was acquired by Shire plc, in January 2014. Mr. Rowland previously held positions of increasing responsibility at the following companies: Biovail Pharmaceuticals, Inc., Breakaway Technologies, Inc., Endo Pharmaceuticals Inc., Pharmacia Corporation, Novartis AG, and Bristol-Myers Squibb Co. Mr. Rowland has served as a member of the board of directors, chairman of the audit committee of Generation Bio since July 2018. Since July 2017, he has served as a member of the board of directors and chairman of the compensation committee and member of the audit committee of Viking Therapeutics, Inc. 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.

Alicia Secor has served as a member of our board of directors since November 2018. Most recently, from August 2016 until its sale to Catalent in August 2018, Ms. Secor served as president and chief executive officer at Juniper Pharmaceuticals, Inc., a diversified public healthcare company. Prior to her role at Juniper, Ms. Secor held several leadership positions in the life sciences industry, including chief commercial officer at Zafgen Inc. from January 2014 to July 2016, senior vice president and chief operating officer at Synageva BioPharma Corp from August 2013 to October 2013, and roles of increasing responsibility at Genzyme from November 1998 to July 2013, including serving as vice president and general manager of the metabolic disease division. Ms. Secor is also a member of the board of directors at GW Pharmaceuticals, plc. and a board member of the Foundation for Prader-Willi Research. She received her B.S. in health administration from the University of New Hampshire and an MBA from Northeastern University. We believe Ms. Secor is qualified to serve on our board because of her experience serving as an officer and director of various publicly traded biotechnology companies.

Family relationships

There are no family relationships among any of our executive officers or directors.

B. Compensation.

For the year ended December 31, 2018, 2017, and 2016, the aggregate compensation accrued or paid to the members of our board of directors and our executive officers for services in all capacities was $13.6 million, $5.1 million, and $0.6 million, respectively.

During and for the years ended December 31, 2018, 2017 and 2016, 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.

The 2016 Plan is administered by our board of directors. The board of directors has the authority to take all actions and make all determinations under the 2016 Plan, to interpret the 2016 Plan and award agreements and to adopt, amend and repeal rules for the administration of the 2016 Plan as it deems advisable, subject to certain limitations imposed under the 2016 Plan, and other applicable laws and stock exchange rules. The plan administrator also has the authority to determine which eligible service providers receive awards, grant awards, set the terms and conditions of all awards under the 2016 Plan, including any vesting and vesting acceleration provisions, subject to the conditions and limitations in the 2016 Plan.

The 2016 Plan provides for the grant of options to purchase our ordinary shares in the future upon written exercise notice. All awards under the 2016 Plan will be set forth in an option certificate, which will detail the terms and conditions of the awards, including any exercise conditions and lapse information.

In connection with certain corporate transactions, including a change of control, our board of directors has broad discretion to take action under the 2016 Plan to prevent the dilution or enlargement of intended benefits, or to facilitate the transaction or event. This includes providing for the assumption or substitution of awards by a successor entity. In addition, in the event of a change in control, the board of directors may accelerate the vesting and exercisability of any option in its discretion. The board of directors may also specify a period of up to 90 days following a change in control during which such options must be exercised and, if not so exercised, such options will terminate.

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 December 31, 2018, options to purchase 10,074,321 shares of common stock remained outstanding under the 2016 Plan. Our board of directors has determined not to make any further awards under the 2016 Plan.

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 became effective on October 30, 2018. 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 close of our initial public offering in November 2018. 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 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 is 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 are those full or part-time officers, employees, non-employee directors and other key persons (including consultants) as selected from time to time by our compensation committee in its discretion.

The 2018 Plan permits the granting of both options to purchase ordinary shares intended to qualify as incentive share options under Section 422 of the Code, and options that do not so qualify. The option exercise price of each option will be determined by our compensation committee but may not be less than 100% of the fair market value of our ordinary shares on the date of grant. The term of each option will be fixed by our compensation committee and may not exceed 10 years from the date of grant. Our compensation committee will determine at what time or times each option may be exercised.

Our compensation committee may award share appreciation rights subject to such conditions and restrictions as it may determine. Share appreciation rights entitle the recipient to ordinary shares, or cash, equal to the value of the appreciation in our share price over the exercise price. The exercise price of each share appreciation right may not be less than 100% of the fair market value of the ordinary shares on the date of grant.

Our compensation committee may award restricted shares and restricted share units to participants subject to such conditions and restrictions as it may determine. These conditions and restrictions may include the achievement of certain performance goals and/or continued employment with us through a specified vesting period. Our compensation committee may also grant ordinary shares that are free from any restrictions under the 2018 Plan. Unrestricted shares may be granted to participants in recognition of past services or other valid consideration and may be issued in lieu of cash compensation due to such participant. Our compensation committee may grant cash bonuses under the 2018 Plan to participants, subject to the achievement of certain performance goals.

The 2018 Plan provides that in the case of, and subject to, the consummation of a "sale event" as defined in the 2018 Plan, all outstanding awards may be assumed, substituted or otherwise continued by the successor entity. To the extent that the successor entity does not assume, substitute or otherwise continue such awards, then (i) all share options and share appreciation rights will automatically become fully exercisable and the restrictions and conditions on all other awards with time-based conditions will automatically be deemed waived, and awards with conditions and restrictions relating to the attainment of performance goals may become vested and non-forfeitable in connection with a sale event in the compensation committee's discretion and (ii) upon the effectiveness of the sale event, the 2018 Plan and all awards will automatically terminate. In the event of such termination, (i) individuals holding options and share appreciation rights will be permitted to exercise such options and share appreciation rights (to the extent exercisable) prior to the sale event; or (ii) we may make or provide for a cash payment to participants holding options and share appreciation rights equal to the difference between the per share cash consideration payable to shareholders in the sale event and the exercise price of the options or share appreciation rights (to the extent then exercisable).

Our board of directors may amend or discontinue the 2018 Plan and our compensation committee may amend the exercise price of options and amend or cancel outstanding awards for purposes of satisfying changes in law or any other lawful purpose but no such action may adversely affect rights under an award without the holder's consent. Certain amendments to the 2018 Plan require the approval of our shareholders. No awards may be granted under the 2018 Plan after the date that is 10 years from the date of shareholder approval.

As of December 31, 2018, options to purchase 129,011 ordinary shares were outstanding under the 2018 Plan and 219,922 unvested performance-based restricted share units were outstanding under the 2018 plan. The total share options and restricted share units outstanding under the 2018 plan as of December 31, 2018 was 349,033.

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 became effective on October 30, 2018. The ESPP is intended to qualify as an "employee share purchase plan" within the meaning of Section 423(b) of the Code. Except where the context indicates otherwise, references hereunder to our ordinary shares shall be deemed to include a number of ADSs equal to the number of ordinary shares. The ESPP initially reserves and authorizes the issuance of up to a total of 850,948 ordinary shares to participating employees. The ESPP provides that the number of shares reserved and available for issuance will automatically increase each January 1, beginning on January 1, 2019 and each January 1 thereafter through January 1, 2028, by the least of (i) 1% of the outstanding number of ordinary shares on the immediately preceding December 31; (ii) 1,500,000 shares or (iii) such number of shares as determined by the ESPP administrator. The number of shares reserved under the ESPP is subject to adjustment in the event of a split-up, share dividend or other change in our capitalization.

All employees who have completed at least 30 days of employment and whose customary employment is for more than 20 hours per week are eligible to participate in the ESPP. However, any employee who owns 5% or more of the total combined voting power or value of all classes of shares is not eligible to purchase shares under the ESPP.

We make one or more offerings each year to our employees to purchase shares under the ESPP. Unless otherwise determined by our compensation committee, offerings usually begin on each January 1 and July 1 and continue for six-month periods, referred to as offering periods. The first offering began on October 30, 2018. 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.

C. Board practices.

Composition of Our Board of Directors

Our board of directors is currently composed of nine members. As a foreign private issuer, under the listing requirements and rules of Nasdaq, we are not required to have independent directors on our board of directors, except that our audit committee is required to consist fully of independent directors, subject to certain phase-in schedules. However, our board of directors has determined that James Geraghty, Joanne Beck, Marc Dunoyer, Jon Ellis, Charles Rowland Jr., Simone Song, and Alicia Secor do not have 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.

In accordance with our Articles of Association, our board members are elected for three-year terms and are subject to retirement by rotation at annual general meetings of shareholders pursuant to our Articles of Association and at least once every three years. A director who retires at an annual general meeting shall be eligible for reappointment if such director is willing to be re-elected. The expiration of the current terms of the members of the Board of Directors and the period each member has served in that term are as follows:

Name	Year Current Term Began	Year Current Term Expires
Joanne Beck	2018	2021
Marc Dunoyer	2018	2020
Jon Ellis	2018	2021
Bobby Gaspar	2018	2019
James Geraghty	2018	2020
Mark Rothera	2018	2020
Charles Rowland Jr.	2018	2021
Alicia Secor	2018	2019
Hong Fang Song	2018	2019

There are no arrangements or understanding between us and any of the members of our board of directors providing for benefits upon termination of their service.

Committees of Our Board of Directors

Our board of directors has three standing committees: an audit committee, a compensation committee and a nominating and corporate governance 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 serves as chairman of the audit committee. The audit committee consists exclusively of members of our board who are financially literate, and Mr. Rowland is considered an "audit committee financial expert" as defined by applicable SEC rules and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations. Our board has determined that all of the members of the audit committee satisfy the "independence" requirements set forth in Rule 10A-3 under the Exchange Act. The audit committee will be governed by a charter that complies with Nasdaq rules.

The audit committee's responsibilities 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., Joanne T. Beck, Ph.D, and Alicia Secor. and Mr. Rowland serves 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 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 and Corporate Governance Committee

The nominating and corporate governance committee consists of James Geraghty and Marc Dunoyer and Mr. Geraghty will serve as chairman of the nominating and corporate governance committee.

The nominating and corporate governance committee's responsibilities 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.

D. Employees.

As of December 31, 2018, we had 180 full-time employees. Of these full-time employees, 80 employees are based in the United Kingdom and European Union and 100 employees are based in the United States. 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.

E. Share ownership.

For information regarding the share ownership of our directors and executive officers, see "Item 6.B – Compensation" and "Item 7.A – Major shareholders."

Item 7. Major Shareholders and Related Party Transactions

A. Major shareholders.

The following table sets forth information with respect to the beneficial ownership of Orchard Therapeutics plc's ordinary shares as of March 15, 2019 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 March 15, 2019. Percentage ownership calculations are based on 85,865,557 ordinary shares outstanding as of March 15, 2019.

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.

Except as otherwise indicated in the table below, addresses of the directors, executive officers and named beneficial owners are in care of Orchard Therapeutics plc, 108 Cannon Street, London EC4N 6EU, United Kingdom.

Name of Beneficial Owner	Number	Percent
5% or Greater Shareholders:		
Entities affiliated with F-Prime(1)	20,407,650	23.8%
GSK(2)	12,455,252	14.5%
Entities affiliated with Deerfield Management Company(3)	8,023,600	9.3%
Entities affiliated with RA Capital Management (4)	4,845,933	5.6%
Scottish Mortgage Investment Trust plc(5)	4,823,325	5.6%
Entities affiliated with Temasek Holdings (Private) Limited (6)	4,319,049	5.0%
Executive Officers and Directors:		
Mark Rothera(7)	977,221	1.1%
Frank E. Thomas(8)	206,313	*
Bobby Gaspar, M.D., Ph.D.(9)	938,782	1.1%
James A. Geraghty(10)	44,391	*
Joanne T. Beck, Ph.D.(11)	9,294	*
Marc Dunoyer(12)	37,179	*
Jon Ellis, Ph.D.	—	*
Charles A. Rowland, Jr.(13)	12,294	*
Hong Fang Song	—	*
Alicia Secor	—	*
All current directors and executive officers as a group (10 persons)(14)	2,225,474	2.6%

* Represents beneficial ownership of less than one percent.

(1) Consists of (i) 10,203,805 of our ordinary shares held of record by F-Prime Capital Partners Healthcare Fund IV LP; and (ii) 10,203,805 of our ordinary 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. 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 held by Deerfield Special Situations Fund, L.P.; (ii) 3,174,708 of our ordinary shares and ADSs held by Deerfield Private Design Fund III, L.P.; (iii) 3,174,708 of our ordinary shares and ADSs held by Deerfield Private Design Fund IV, L.P.; and (iv) 1,209,434 of our ordinary shares and ADSs held by Deerfield Partners, L.P. Deerfield Mgmt, L.P. is the general partner of Deerfield Special Situations Fund, L.P and Deerfield Partners, 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. and Deerfield Partners, 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) Based solely on a Schedule 13G filed jointly filed by RA Capital Management, LLC and Dr. Peter Kolchinsky on February 14, 2019. Consists of 4,845,933 of our ADSs held by RA Capital Healthcare Fund, L.P. RA Capital Management, LLC is the general partner of RA Capital Healthcare Fund, L.P. Dr. Kolchinsky is the manager of RA Capital Management, LLC. Each of RA Capital Management, LLC and Dr. Kolchinksy may be deemed to beneficially own the ADSs owned by RA Capital Healthcare Fund, L.P., and each of RA Capital Management, LLC and Dr. Kolchinsky expressly disclaim beneficial ownership of such securities. The address of RA Capital Management, LLC is 20 Park Plaza, Suite 1200, Boston, MA 02116.

(5) Consists of (i) 4,823,325 of our ordinary shares and ADSs 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.

(6) Based solely on a Schedule 13G filed jointly filed by Temasek Holdings (Private) Limited, or Temasek, Fullerton Management Pte Ltd, or FMPL, and Temasek Life Sciences Private Limited, or TLS, on November 13, 2018. Consists of (i) 3,319,049 ordinary shares and ADRs held by TLS Beta Pte. Ltd, and (ii) 1,000,000 ADSs held by V-Sciences Investments Pte Ltd. TLS Beta Pte. Ltd and V-Sciences Investments Pte Ltd are wholly-owned subsidiaries of TLS which is a wholly owned subsidiary of FMPL, which is a wholly owned subsidiary of Temasek. Each of TLS, FMPL, and Temasek, through the ownership described herein, may be deemed to beneficially own the shares held by TLS Beta Pte. Ltd and V-Sciences Investments Pte Ltd. The address of Temasek is 60B Orchard Road, #06-18 Tower 2, The Atrium@Orchard, Singapore 238891.

(7) Consists of (i) 90,304 of our ordinary shares and ADSs and (ii) 886,917 or our ordinary shares issuable upon exercise of options within 60 days of March 15, 2019.

(8) Consists of (i) 14,294 of our ordinary shares and (ii) 192,019 of our ordinary shares issuable upon exercise of options within 60 days of March 15, 2019.

(9) Consists of (i) 417,319 of our ordinary shares and (ii) 521,463 of our ordinary shares issuable upon exercise of options within 60 days of March 15, 2019.

(10) Consists of 44,391 of our ordinary shares and ADSs.

(11) Consists of 9,294 of our ordinary shares and ADSs.

(12) Consists of 37,179 of our ordinary shares and ADSs.

(13) Consists of 12,294 of our ordinary shares and ADSs.

(14) Consists of (i) 625,075 of our ordinary shares and ADSs and (ii) 1,600,399 of our ordinary shares issuable upon exercise of options within 60 days of March 15, 2019.

To our knowledge, there has been no significant change in the percentage ownership held by the major shareholders listed above since March 15, 2019.

B. Related party transactions.

Since January 1, 2018, we have engaged in the following transactions with our directors, executive officers or holders of more than 10% of our outstanding share capital and their affiliates, which we refer to as our related parties.

GSK asset purchase and license agreement

On April 11, 2018, we entered the GSK Agreement pursuant to which GSK transferred to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first approved gene therapy by the EMA, two late-stage clinical gene therapy programs in ongoing registrational studies: OTL-200 for MLD and OTL-103 for WAS; and OTL-300, a clinical-stage gene therapy program for TDBT. In addition, under this agreement, GSK novated to us their R&D Agreement with the Telethon-OSR.

Upon execution of the agreement, we paid GSK a one-time upfront fee of £10.0 million, and we issued GSK 12,455,252 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. We may pay up to an aggregate of £90.0 million in 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 Item 4.B “Business — License agreements — GSK asset purchase and license agreement” for further information regarding the GSK Agreement.

In connection with this agreement, we also entered into (i) a transitional services agreement with GSK on April 11, 2018, pursuant to which GSK has agreed to provide us certain transitional services in connection with the transfer of the assets acquired under the GSK Agreement, and (ii) an inventory sale agreement with GSK on April 11, 2018, pursuant to GSK agreed to transfer certain inventory related to the assets acquired under the GSK Agreement.

As a result of the GSK Agreement, GSK is currently a greater than 10% 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 our initial public offering in November 2018 until such time as we obtain marketing approval and commercially launch OTL-200 for MLD.

Subscription of our Series C convertible preferred shares

In August 2018, we sold an aggregate of 13,942,474 shares of our Series C convertible preferred shares at a purchase price of $10.76 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
Mark Rothera(1)	24,979	$	268,796
Frank E. Thomas(2)	9,294	$	100,000
James A. Geraghty(3)	34,391	$	370,000
Joanne T. Beck, Ph.D.(4)	9,294	$	100,000
Marc Dunoyer(5)	37,179	$	400,000
Charles A. Rowland, Jr.(6)	9,294	$	100,000

(1) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

(2) Mr. Thomas is our Chief Financial Officer and Chief Business Officer.

(3) Mr. Geraghty is the chairman of our board of directors.

(4) Dr. Beck is a member of our board of directors.

(5) Mr. Dunoyer is a member of our board of directors.

(6) Mr. Rowland, Jr. is a member of our board of directors.

Participation in Our Initial Public Offering

In November 2018, we sold an aggregate of 16,103,572 ADS's in our IPO at a price of $14.00 per share. The following table summarizes purchases of ADSs in our IPO by related persons:

Shareholder	ADRs in IPO	Total Purchase Price
Mark Rothera(1)	18,500	$ 259,000
Frank E. Thomas(2)	5,000	$ 70,000
James A. Geraghty(3)	10,000	$ 140,000
Charles A. Rowland, Jr.(4)	3,000	$ 42,000

(1) Mr. Rothera is our President, Chief Executive Officer and a member of our board of directors.

(2) Mr. Thomas is our Chief Financial Officer and Chief Business Officer.

(3) Mr. Geraghty is the chairman of our board of directors.

(4) Mr. Rowland is a member of our board of directors.

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 have entered into a deed of indemnity with each of our directors and executive officers. 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

We have adopted a written related party transactions policy that such transactions must be approved by our audit committee. This policy became effective on October 30, 2018, the date on which our registration statement on Form F-1 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.

C. Interests of experts and counsel.

Not applicable.

Item 8. Financial Information

A. Consolidated Statements and Other Financial Information.

See "Item 18. Financial Statements."

B. Significant Changes.

Not applicable.

Item 9. The Offer and Listing.

A. Offer and listing details.

Our ADSs began trading on the Nasdaq Global Select Market under the symbol “ORTX” on October 31, 2018.

On March 21, 2019, the last reported sale price of the ADSs on The Nasdaq Global Select Market was $17.00 per ADS.

B. Plan of distribution.

Not applicable.

C. Markets.

The ADSs have been listed on the Nasdaq Global Select Market under the symbol “ORTX” since October 31, 2018.

D. Selling shareholders

Not applicable.

E. Dilution.

Not applicable.

F. Expenses of the issue.

Not applicable.

Item 10. Additional Information.

A. Share capital.

Not applicable.

B. Memorandum and articles of association.

The information set forth in our prospectus dated October 31, 2018, filed with the SEC pursuant to Rule 424(b), under the headings “Description of share capital and articles of association—Issued share capital,” “Description of share capital and articles of association—Ordinary shares,” “Description of share capital and articles of association—Registered shares,” “Description of share capital and articles of association—Preemptive rights,” “Description of share capital and articles of association—Post-IPO articles of association,” “Description of share capital and articles of association—Other relevant laws and regulations,” “Description of share capital and articles of association—Differences in corporate law,” and “Service of process and enforcement of liabilities” is incorporated herein by reference.

C. Material contracts.

Except as otherwise disclosed in this Annual Report (including the exhibits thereto), we are not currently, and have not been in the last two years, party to any material contract, other than contracts entered into in the ordinary course of our business.

D. Exchange controls.

There are no governmental laws, decrees, regulations or other legislation in the United Kingdom that may affect the import or export of capital, including the availability of cash and cash equivalents for use by us, or that may affect the remittance of dividends, interest, or other payments by us to non-resident holders of our ordinary shares or ADSs, other than withholding tax requirements. There is no limitation imposed by the laws of England and Wales or our articles of association on the right of non-residents to hold or vote shares.

E. Taxation.

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 beneficial owners of ADSs.

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 holds our ordinary shares or ADSs as a capital asset for tax purposes (generally, property held for investment). In addition, it does not describe all of the tax consequences that may be relevant in light of a U.S. Holder's particular circumstances, including state and local tax consequences, estate tax consequences, alternative minimum tax consequences, the potential application of the Medicare contribution tax, and tax consequences applicable to U.S. Holders subject to special rules, such as:

- banks, insurance companies, and certain other financial institutions;
- U.S. expatriates and certain former citizens or long-term residents of the United States;
- dealers or traders in securities who use a mark-to-market method of tax accounting;
- persons holding ordinary shares or ADSs as part of a hedging transaction, "straddle," wash sale, conversion transaction or integrated transaction or persons entering into a constructive sale with respect to ordinary shares or ADSs;
- persons whose "functional currency" for U.S. federal income tax purposes is not the U.S. dollar;
- brokers, dealers or traders in securities, commodities or currencies;
- tax-exempt entities or government organizations;
- S corporations, partnerships, or other entities or arrangements classified as partnerships for U.S. federal income tax purposes;
- regulated investment companies or real estate investment trusts;
- persons who acquired our ordinary shares or ADSs pursuant to the exercise of any employee stock option or otherwise as compensation; and
- persons holding our ordinary shares or ADSs in connection with a trade or business, permanent establishment, or fixed base outside the United States.

If an entity that is classified as a partnership for U.S. federal income tax purposes holds ordinary shares or ADSs, the U.S. federal income tax treatment of a partner will generally depend on the status of the partner and the activities of the partnership. Partnerships holding ordinary shares or ADSs and partners in such partnerships are encouraged to consult their tax advisers as to the particular U.S. federal income tax consequences of holding and disposing of ordinary shares or ADSs.

The discussion is based on the Code, administrative pronouncements, judicial decisions, final, temporary and proposed Treasury Regulations, and the income tax treaty between the United Kingdom and the United States, or the Treaty, all as of the date hereof, changes to any of which may affect the tax consequences described herein—possibly with retroactive effect.

A “U.S. Holder” is a holder who, for U.S. federal income tax purposes, is a beneficial owner of ordinary shares or ADSs and is:

(i) An individual who is a citizen or individual resident of the United States;

(ii) a corporation, or other entity taxable as a corporation, created or organized in or under the laws of the United States, any state therein or the District of Columbia;

(iii) an estate the income of which is subject to U.S. federal income taxation regardless of its source; or

(iv) a trust if (1) a U.S. court is able to exercise primary supervision over the administration of the trust and one or more U.S. persons have authority to control all substantial decisions of the trust or (2) the trust has a valid election to be treated as a U.S. person under applicable U.S. Treasury Regulations.

The discussion below assumes that the representations contained in the deposit agreement are true and that the obligations in the deposit agreement and any related agreement will be complied with in accordance with their terms. Generally, a holder of an ADS should be treated for U.S. federal income tax purposes as holding the ordinary shares represented by the ADS. Accordingly, no gain or loss will be recognized upon an exchange of ADSs for ordinary shares. The U.S. Treasury has expressed concerns that intermediaries in the chain of ownership between the holder of an ADS and the issuer of the security underlying the ADS may be taking actions that are inconsistent with the beneficial ownership of the underlying security. Accordingly the creditability of foreign taxes, if any, as described below, could be affected by actions taken by intermediaries in the chain of ownership between the holders of ADSs and our company if as a result of such actions the holders of ADSs are not properly treated as beneficial owners of the underlying ordinary shares. These actions would also be inconsistent with the claiming of the reduced tax rate, described below, applicable to dividends received by certain non-corporate holders.

PERSONS CONSIDERING AN INVESTMENT IN ORDINARY SHARES OR ADSs SHOULD CONSULT THEIR OWN TAX ADVISORS AS TO THE PARTICULAR TAX CONSEQUENCES APPLICABLE TO THEM RELATING TO THE ACQUISITION, OWNERSHIP AND DISPOSITION OF THE ORDINARY SHARES OR ADSs, INCLUDING THE APPLICABILITY OF U.S. FEDERAL, STATE AND LOCAL TAX LAWS.

PFIC Rules

If we are classified as a PFIC in any taxable year, a U.S. Holder will be subject to special rules generally intended to reduce or eliminate any benefits from the deferral of U.S. federal income tax that a U.S. Holder could derive from investing in a non-U.S. company that does not distribute all of its earnings on a current basis.

A non-U.S. corporation will be classified as a PFIC for any taxable year in which, after applying certain look-through rules, either:

- at least 75% of its gross income is passive income (such as interest income); or
- at least 50% of its gross assets (determined on the basis of a quarterly average) is attributable to assets that produce passive income or are held for the production of passive income.

We will be treated as owning our proportionate share of the assets and earning our proportionate share of the income of any other corporation, the equity of which we own, directly or indirectly, 25% or more (by value).

We do not believe that we were a PFIC in the 2018 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a “controlled foreign corporation” for any taxable year (see discussion below in “Controlled foreign corporation considerations”), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC, or may be treated as a PFIC in the future.

If we are classified as a PFIC in any year with respect to which a U.S. Holder owns the ordinary shares or ADSs, we will continue to be treated as a PFIC with respect to such U.S. Holder in all succeeding years during which the U.S. Holder owns the ordinary shares or ADSs, regardless of whether we continue to meet the tests described above unless (i) we cease to be a PFIC and the U.S. Holder has made a "deemed sale" election under the PFIC rules, or (ii) the U.S. Holder makes a Qualified Electing Fund Election, or QEF Election, with respect to all taxable years during such U.S. Holders holding period in which we are a PFIC. If the "deemed sale" election is made, a U.S. Holder will be deemed to have sold the ordinary shares or ADSs the U.S. Holder holds at their fair market value and any gain from such deemed sale would be subject to the rules described below. After the deemed sale election, so long as we do not become a PFIC in a subsequent taxable year, the U.S. Holder's ordinary shares or ADSs with respect to which such election was made will not be treated as shares in a PFIC and the U.S. Holder will not be subject to the rules described below with respect to any "excess distribution" the U.S. Holder receives from us or any gain from an actual sale or other disposition of the ordinary shares or ADSs. U.S. Holders should consult their tax advisors as to the possibility and consequences of making a deemed sale election if we cease to be a PFIC and such election becomes available.

For each taxable year we are treated as a PFIC with respect to U.S. Holders, U.S. Holders will be subject to special tax rules with respect to any "excess distribution" such U.S. Holder receives and any gain such U.S. Holder recognizes from a sale or other disposition (including, under certain circumstances, a pledge) of ordinary shares or ADSs, unless (i) such U.S. Holder makes a QEF Election or (ii) our ordinary shares or ADSs constitute "marketable" securities, and such U.S. Holder makes a mark-to-market election as discussed below. Distributions a U.S. Holder receives in a taxable year that are greater than 125% of the average annual distributions a U.S. Holder received during the shorter of the three preceding taxable years or the U.S. Holder's holding period for the ordinary shares or ADSs will be treated as an excess distribution. Under these special tax rules:

- the excess distribution or gain will be allocated ratably over a U.S. Holder's holding period for the ordinary shares or ADSs;
- the amount allocated to the current taxable year, and any taxable year prior to the first taxable year in which we became a PFIC, will be treated as ordinary income; and
- the amount allocated to each other year will be subject to the highest tax rate in effect for that year and the interest charge generally applicable to underpayments of tax will be imposed on the resulting tax attributable to each such year.

The tax liability for amounts allocated to years prior to the year of disposition or "excess distribution" cannot be offset by any net operating losses for such years, and gains (but not losses) realized on the sale of the ordinary shares or ADSs cannot be treated as capital, even if a U.S. Holder holds the ordinary shares or ADSs as capital assets.

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF Election. In addition, if we are a PFIC, a U.S. Holder will generally be subject to similar rules with respect to distributions we receive from, and our dispositions of the stock of, any of our direct or indirect subsidiaries that also are PFICs, as if such distributions were indirectly received by, and/or dispositions were indirectly carried out by, such U.S. Holder. U.S. Holders should consult their tax advisors regarding the application of the PFIC rules to our subsidiaries.

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are "marketable." Ordinary shares or ADSs will be marketable if they are "regularly traded" on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, 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 INVESTORS 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 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. 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 Annual Report (both of which are subject to change at any time, possibly with retrospective effect) relating to the holding of ADSs. It does not constitute legal or tax advice and does not purport to be a complete analysis of all U.K. tax considerations relating to the holding of ADSs, or all of the circumstances in which holders of ADSs may benefit from an exemption or relief from U.K. taxation. It is written on the basis that the company is and remains solely resident in the U.K. for tax purposes and will therefore be subject to the U.K. tax regime and not the U.S. tax regime save as set out above under "Material U.S. federal income tax considerations for U.S. Holders."

Except to the extent that the position of non-U.K. resident persons is expressly referred to, this guide relates only to persons who are resident (and in the case of individuals, domiciled or deemed domiciled) for tax purposes solely in the U.K. and do not have a permanent establishment, branch or agency (or equivalent) in any other jurisdiction with which the holding of the ADSs is connected, or U.K. Holders, who are absolute beneficial owners of the ADSs (and do not hold the ADSs through an Individual Savings Account or a Self-Invested Personal Pension) and any dividends paid in respect of the ADSs or underlying ordinary shares (where the dividends are regarded for U.K. tax purposes as that person's own income). It is assumed that for the purposes of this guide that a holder of an ADS is the beneficial owner of the underlying ordinary share and any dividend income for U.K. direct tax purposes.

This guide may not relate to certain classes of U.K. Holders, such as (but not limited to):

- persons who are connected with the company;
- financial institutions;
- insurance companies;
- charities or tax-exempt organizations;
- collective investment schemes;
- pension schemes;
- brokers or dealers in securities or persons who hold ADSs otherwise than as an investment;
- persons who have (or are deemed to have) acquired their ADSs by virtue of an office or employment or who are or have been officers or employees of the company or any of its affiliates; and
- individuals who are subject to U.K. taxation on a remittance basis.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN U.K. TAX CONSIDERATIONS AND ARE INTENDED AS A GENERAL GUIDE ONLY. IT IS RECOMMENDED THAT ALL HOLDERS OF ADSs OBTAIN ADVICE AS TO THE CONSEQUENCES OF THE ACQUISITION, OWNERSHIP AND DISPOSAL OF THE ADSs IN THEIR OWN PARTICULAR CIRCUMSTANCES FROM THEIR OWN TAX ADVISORS. IN PARTICULAR, NON-U.K. RESIDENT OR DOMICILED PERSONS ARE ADVISED TO CONSIDER THE POTENTIAL IMPACT OF ANY RELEVANT DOUBLE TAXATION AGREEMENTS.

Dividends

Withholding Tax

Dividends paid by the company will not be subject to any withholding or deduction for or on account of U.K. tax.

Income Tax

An individual U.K. Holder may, depending on his or her particular circumstances, be subject to U.K. tax on dividends received from the company. An individual holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. income tax on dividends received from the company unless he or she carries on (whether solely or in partnership) a trade, profession or vocation in the U.K. through a permanent establishment, branch or agency to which the ADSs are attributable.

Dividend income is treated as the top slice of the total income chargeable to U.K. income tax. An individual U.K. Holder who receives a dividend in the 2018/2019 tax year will be entitled to a tax-free allowance of £2,000. Dividend income in excess of this tax-free allowance will be charged at 7.5% for basic rate taxpayers, 32.5% for higher rate taxpayers, and 38.1% for additional rate taxpayers.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to U.K. corporation tax on dividends received from the company unless it carries on (whether solely or in partnership) a trade in the United Kingdom through a permanent establishment to which the ADSs are attributable.

Corporate U.K. Holders should not be subject to U.K. corporation tax on any dividend received from the company so long as the dividends qualify for exemption, which should be the case, although certain conditions must be met. If the conditions for the exemption are not satisfied, or such U.K. Holder elects for an otherwise exempt dividend to be taxable, U.K. corporation tax will be chargeable on the amount of any dividends (at the current rate of 19%).

Chargeable gains

A disposal or deemed disposal of ADSs by a U.K. Holder may, depending on the U.K. Holder's circumstances and subject to any available exemptions or reliefs (such as the annual exemption), give rise to a chargeable gain or an allowable loss for the purposes of U.K. capital gains tax and corporation tax on chargeable gains.

If an individual U.K. Holder who is subject to U.K. income tax at either the higher or the additional rate is liable to U.K. capital gains tax on the disposal of ADSs, the applicable rate will be 20% (2018/2019). For an individual U.K. Holder who is subject to U.K. income tax at the basic rate and liable to U.K. capital gains tax on such disposal, the applicable rate would be 10% (2018/2019), save to the extent that any capital gains exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (2018/2019).

If a corporate U.K. Holder becomes liable to U.K. corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of U.K. corporation tax (currently 19%) would apply.

A holder of ADSs which is not resident for tax purposes in the U.K. should not normally be liable to U.K. capital gains tax or corporation tax on chargeable gains on a disposal (or deemed disposal) of ADSs, unless the person is carrying on (whether solely or in partnership) a trade, profession or vocation in the United Kingdom through a permanent establishment, branch or agency to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the U.K. for a period of less than five years and who disposes of ADSs during that period may be liable on his or her return to the U.K. to U.K. tax on any capital gain realized (subject to any available exemption or relief).

Stamp duty and stamp duty reserve tax

The discussion below relates to the holders of our ordinary shares or ADSs wherever resident, however it should be noted that special rules may apply to certain persons such as market makers, brokers, dealers or intermediaries.

Issue of Ordinary Shares

No U.K. stamp duty or stamp duty reserve tax, or SDRT, is payable on the issue of the underlying ordinary shares in the company.

Transfers of Ordinary Shares

An unconditional agreement to transfer ordinary shares will normally give rise to a charge to SDRT at the rate of 0.5% of the amount or value of the consideration payable for the transfer. The purchaser of the shares is liable for the SDRT. Transfers of ordinary shares in certificated form are generally also subject to stamp duty at the rate of 0.5% of the amount or value of the consideration given for the transfer (rounded up to the next £5.00). Stamp duty is normally paid by the purchaser. The charge to SDRT will be cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

An unconditional agreement to transfer ordinary shares to, or to a nominee or agent for, a person whose business is or includes the issue of depositary receipts or the provision of clearance services will generally be subject to SDRT (and, where the transfer is effected by a written instrument, stamp duty) at a higher rate of 1.5% of the amount or value of the consideration given for the transfer unless the clearance service has made and maintained an election under section 97A of the U.K. Finance Act 1986, or a section 97A election. It is understood that HMRC regards the facilities of DTC as a clearance service for these purposes and we are not aware of any section 97A election having been made by the DTC.

Based on current published HMRC practice following recent case law in respect of the European Council Directives 69/335/EEC and 2009/7/EC, or the Capital Duties Directives, no SDRT is generally payable where the transfer of ordinary shares to a clearance service or depositary receipt system outside the European Union is an integral part of an issue of share capital (although the relevant judgment refers to transfers which are integral to the raising of capital). In addition, a recent Court of Justice of the European Union judgment (Air Berlin plc v HMRC (2017)) held on the relevant facts that the Capital Duties Directives preclude the taxation of a transfer of legal title to shares for the sole purpose of listing those shares on a stock exchange which does not impact the beneficial ownership of the shares, but, as yet, the U.K. domestic law and HMRC's published practice remain unchanged and, accordingly, we anticipate that amounts on account of SDRT will continue to be collected by the depositary receipt issuer or clearance service. Holders of ordinary shares should consult their own independent professional advisers before incurring or reimbursing the costs of such a 1.5% SDRT charge. Any stamp duty or SDRT payable on a transfer of ordinary shares to a depositary receipt system or clearance service will in practice generally be paid by the participants in the clearance service or depositary receipt system.

Transfers of ADSs

No U.K. stamp duty will in practice be payable on a written instrument transferring an ADS provided that the instrument of transfer is executed and remains at all times outside the United Kingdom. Where these conditions are not met, the transfer of, or agreement to transfer, an ADS could, depending on the circumstances, attract a charge to U.K. stamp duty at the rate of 0.5% of the value of the consideration.

No SDRT will be payable in respect of an agreement to transfer an ADS.

F. Dividends and paying agents.

Not applicable.

G. Statement by experts.

Not applicable.

H. Documents on display.

We are subject to the information reporting requirements of the Exchange Act applicable to foreign private issuers and file reports under those requirements with the SEC. Those reports may be inspected without charge at the locations described below. As a foreign private issuer, we are exempt from the rules under the Exchange Act related to the furnishing and content of proxy statements, and our officers, directors and principal shareholders are exempt from the reporting and short-swing profit recovery provisions contained in Section 16 of the Exchange Act. In addition, we are not required under the Exchange Act to file periodic reports and financial statements with the SEC as frequently or as promptly as United States 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 Annual Report. We have included our website address in this Annual Report solely as an inactive textual reference.

You may also review a copy of this Annual Report, including exhibits and any schedule filed herewith, and obtain copies of such materials at prescribed rates, at the SEC's Public Reference Room in Room 1580, 100 F Street, NE, Washington, D.C. 20549-0102. You may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains a website (www.sec.gov) that contains reports, proxy and information statements and other information regarding registrants, such as us, that file electronically with the SEC.

With respect to references made in this Annual Report to any contract or other document of our company, such references are not necessarily complete and you should refer to the exhibits attached or incorporated by reference to this Annual Report for copies of the actual contract or document.

I. Subsidiary Information.

Not applicable.

Item 11. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate sensitivity

As of December 31, 2018, we had cash of $335.8 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 December 31, 2018, we had no debt outstanding and are therefore not subject to interest rate risk related to debt.

Foreign currency exchange risk

The Company is exposed to foreign currency exchange risk because it currently operates in the United Kingdom and the United States. The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the ultimate parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expense cash in U.S. dollars, and expects to continue to do so in the future. Monetary assets and liabilities denominated in currencies other than the functional currency are translated into the functional currency of the relevant entity 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 a foreign currency gain of $4.4 million and a $1.2 million loss for the years ended December 31, 2018 and 2017, respectively. These foreign currency transaction gains and losses are included in other expense in our consolidated statements of operations and comprehensive loss.

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.

Item 12. Description of Securities Other than Equity Securities.

A. Debt Securities

Not applicable.

B. Warrants and Rights.

Not applicable.

C. Other Securities.

Not applicable.

D. American Depositary Shares.

Citibank, N.A., or Citibank, as depositary bank, registers and delivers our American Depositary Shares, also referred to as 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. A copy of the deposit agreement may be obtained 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.

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

Item 13. Defaults, Dividend Arrearages and Delinquencies.

Not applicable.

Item 14. Material Modifications to the Rights of Security Holders and Use of Proceeds.

Not applicable.

Item 15. Controls and Procedures.

A. Disclosure Controls and Procedures.

Our management, with the participation of our Chief Executive Officer and Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) as of December 31, 2018. Based on such evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2018, our disclosure controls and procedures were not effective because of the material weakness described below. We are undertaking the remedial steps to address the material weakness in our disclosure controls and procedures as set forth below under "Remediation of Previously Identified Material Weakness, and Management's Plan for Remediation of Remaining Material Weakness."

B. Management's annual report on internal control over financial reporting.

This Annual Report does not include a report of management's assessment regarding internal control over financial reporting due to a transition period established by the SEC's rules for newly public companies.

C. Attestation report of the registered public accounting firm

This Annual Report does not include an attestation report of our registered public accounting firm due to a transition period established by rules of the SEC for newly public companies. Additionally, our independent registered public accounting firm will not be required to opine on our internal control over financial reporting until we are no longer an emerging growth company.

D. Changes in internal control over financial reporting.

Other than disclosed below, there were no changes in our internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) that occurred during the period covered by this Annual Report that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Remediation of Previously Identified Material Weakness, and Management's Plan for Remediation of Remaining Material Weakness

Our management previously identified deficiencies that were concluded to represent material weaknesses in our internal control over financial reporting where we did not design or implement sufficient processes, controls and other review procedures performed by personnel familiar with U.S. GAAP to evaluate (i) the recognition and accrual of research and development related expenses and reimbursements and (ii) the recognition of assets and liabilities contingent on future events. SEC guidance regarding management's report on internal control over financial reporting defines a material weakness as a deficiency or combination of deficiencies in internal control over financial reporting, such that there is a reasonable possibility that a material misstatement of our annual or interim financial statements will not be prevented or detected and corrected on a timely basis.

With the oversight of senior management and our audit committee, we continue to evaluate our internal control over financial reporting and have taken several remedial actions to address the material weaknesses that have been identified:

- We hired a full-time Chief Financial Officer in January 2018, who has significant experience with establishing appropriate financial reporting policies and experience in supporting, designing and implementing effective internal controls over financial reporting;

- We have implemented formal procedures relating to period end financial reporting and the identification and resolution of non-routine transactions, and;
- We have hired additional finance and accounting personnel with appropriate expertise to perform specific functions and intend to hire additional personnel to further assist in the implementation of improved processes and internal controls, build our financial management and reporting infrastructure and further develop and document our accounting policies and financial reporting procedures, including ongoing senior management review and audit committee oversight.

We have determined that through the actions described above we have remediated the previously identified material weakness associated with our accounting for assets and liabilities contingent on future events.

We have taken and plan to continue to take actions, as described above, that will improve our overall system of internal control over financial reporting. We expect that these measures will be sufficient to remediate the remaining material weakness. However, these measures are still ongoing and changes to internal controls over financial reporting need to operate for a period of time in order for management to evaluate and test whether the internal control changes are effective.

Item 16A. Audit committee financial expert.

The audit committee consists of Charles A. Rowland, Jr., Marc Dunoyer and Jon Ellis, Ph.D. Mr. Rowland will serve as chairman of the audit committee. The audit committee consists exclusively of members of our board who are financially literate, and Mr. Rowland is considered an "audit committee financial expert" as defined by applicable SEC rules and has the requisite financial sophistication as defined under the applicable Nasdaq rules and regulations. Our board has determined that all of the members of the audit committee satisfy the "independence" requirements set forth in Rule 10A-3 under the Exchange Act.

Item 16B. Code of 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 Annual Report and is not incorporated by reference herein.

Item 16C. Principal Accountant Fees and Services.

PricewaterhouseCoopers LLP has served as our independent registered public accountant since June 2018 and has audited our consolidated financial statements for the years ended December 31, 2018, 2017 and 2016, which appear elsewhere in this Annual Report.

The following table shows the aggregate fees for services rendered by PricewaterhouseCoopers LLP to us and our subsidiaries, in the fiscal year ended December 31, 2018 (presented in thousands).

Fee Category	Year Ended December 31,	
	2018	2017
	(in thousands)	
Audit fees	$ 2,970	$ —
Audit-related fees	—	—
Tax fees	—	—
All other fees	50	—
Total	$ 3,020	$ —

Audit Fees. Audit fees consisted $1,063 in fees for the audit and review of our annual and interim financial statements included in our registration statement for the periods ended December 31, 2016 and 2017, and June 30, 2017 and 2018. Audit fees also include $513 in fees for the audit and review of our annual financial statements included in this Annual Report for the year ended December 31, 2018. Additionally, Audit fees consists of $1,394 of fees billed in connection with our initial public offering that closed in November 2018.

All other fees. All other fees represent $47 in consulting costs associated with our corporate reorganization and $3 for access to PricewaterhouseCoopers LLP online accounting research tool.

Audit Committee Pre-Approval Policies and Procedures

Our audit committee reviews and pre-approves the scope and the cost of audit services related to us and permissible non-audit services performed by the independent auditors, other than those for *de minimis* services which are approved by the audit committee prior to the completion of the audit. All of the services related to our company provided by PricewaterhouseCoopers LLP during the last fiscal year have been approved by the audit committee.

Item 16D. Exemptions from the Listing Standards for Audit Committees.

The Nasdaq listing rules mandated by Rule 10A-3(b) of the Exchange Act require, among other things, that each member of the audit committee be independent. A company listing in connection with its IPO may phase in its compliance with the independent committee requirement pursuant to Rule 10A-3(b)(1)(iv)(A) of the Exchange Act. Accordingly, a company listing in connection with its IPO is permitted to phase in its compliance with the independent committee requirements as follows: (1) one independent member at the time of listing; (2) a majority of independent members within 90 days of listing; and (3) all independent members within one year of listing.

Immediately after our IPO, our audit committee consisted of Charles A. Rowland, Marc Dunoyer and Jon Ellis, Ph.D. Our audit committee currently consists of these same individuals. Mr. Rowland, Mr. Dunoyer, and Mr. Ellis meet the independence standards of Nasdaq Listing Rule 5605(a)(2) and satisfy the criteria for independence set forth in Section 10A(m)(3) of the Exchange Act. Our board has determined that all of the members of the audit committee satisfy the “independence” requirements set forth in Rule 10A-3under the Exchange Act. The audit committee will be governed by a charter that complies with Nasdaq rules.

Item 16E. Purchases of Equity Securities by the Issuer and Affiliated Purchasers.

Not applicable.

Item 16F. Change in Registrant’s Certifying Accountant.

Our statutory financial statements were audited by Blick Rothenberg Audit LLP, or Blick Rothenberg for the years ended December 31, 2016 and 2017 as our group statutory auditor under U.K. GAAP in accordance with International Standards on Auditing (United Kingdom and Ireland). At the time Blick Rothenberg performed audit services for us, we were not a public company and were not subject to SEC regulations. In preparation for our initial public offering, on August 2, 2018, we engaged PricewaterhouseCoopers LLP to audit our financial statements for the years ended December 31, 2016 and 2017 under U.S. GAAP in accordance with standards of the U.S. Public Company Accounting Oversight Board. These financial statements, including PricewaterhouseCoopers audit report thereon, are included in this Annual Report. The engagement of PricewaterhouseCoopers LLP was approved by our board of directors. On December 14, 2018, our Audit Committee appointed PricewaterhouseCoopers LLP as our group statutory auditor, and we dismissed Blick Rothenberg.

For our fiscal years ended December 31, 2016 and 2017 and the subsequent interim periods through December 14, 2018, no report by Blick Rothenberg related to our statutory financial statements under U.K. GAAP contained an adverse opinion or a disclaimer of opinion, or was qualified or modified as to uncertainty, audit scope or accounting principles. During such time period, there were no disagreements or reportable events (as defined by 20-F 16Fa(V)(a)) between us and Blick Rothenberg on any matter of accounting principles or practices, financial statement disclosure, or auditing scope or procedure.

We have provided Blick Rothenberg with a copy of the disclosure contained in this annual report, which was received by Blick Rothenberg on March 6, 2019. Blick Rothenberg have furnished a letter addressed to the SEC which is filed as an exhibit to this Annual Report on Form 20-F stating agreement with the statements made in this Annual Report.

Item 16G. Corporate Governance.

We are a “foreign private issuer,” as defined by the SEC. As a result, in accordance with Nasdaq listing requirements, we may rely on home country governance requirements and certain exemptions thereunder rather than complying with Nasdaq corporate governance standards. While we voluntarily follow most Nasdaq corporate governance rules, we may choose to take advantage of the following limited exemptions:

- exemption from filing quarterly reports on Form 10-Q containing unaudited financial and other specified information or current reports on Form 8-K upon the occurrence of specified significant events;
- exemption from Section 16 rules requiring insiders to file public reports of their stock ownership and trading activities and liability for insiders who profit from trades in a short period of time, which will provide less data in this regard than shareholders of U.S. companies that are subject to the Exchange Act;
- exemption from the Nasdaq requirement requiring disclosure of any waivers of the Code of Business Conduct and Ethics, or Code of Ethics, for directors and officers;
- exemption from the requirement to obtain shareholder approval for certain issuances of securities, including shareholder approval of share option plans;
- exemption from the requirement that our audit committee have review and oversight over all "related party transactions," as defined in Item 7.B of Form 20-F;
- exemption from the requirement that our board have a compensation committee that is composed entirely of independent directors with a written charter addressing the committee's purpose and responsibilities; and
- exemption from the requirement to have independent director oversight of director nominations.

We intend to follow U.K. corporate governance practices in lieu of Nasdaq corporate governance requirements as follows:

- We do not intend to follow Nasdaq Rule 5620(c) regarding quorum requirements applicable to meetings of shareholders. Such quorum requirements are not required under English law. In accordance with generally accepted business practice, our Articles of Association will provide alternative quorum requirements that are generally applicable to meetings of shareholders.
- We do not intend to follow Nasdaq Rule 5605(b)(2), which requires that independent directors regularly meet in executive sessions where only independent directors are present. Our independent directors may choose to meet in executive sessions at their discretion.

Although we may rely on certain home country corporate governance practices, we must comply with Nasdaq's Notification of Noncompliance requirement (Nasdaq Rule 5625) and the Voting Rights requirement (Nasdaq Rule 5640). Further, we must have an audit committee that satisfies Nasdaq Rule 5605(c)(3), which addresses audit committee responsibilities and authority and requires that the audit committee consist of members who meet the independence requirements of Nasdaq Rule 5605(c)(2)(A)(ii).

Because we are a foreign private issuer, our directors and senior management are not subject to short-swing profit and insider trading reporting obligations under Section 16 of the Exchange Act. They will, however, be subject to the obligations to report changes in share ownership under Section 13 of the Exchange Act and related SEC rules.

We intend to take all actions necessary for us to maintain compliance as a foreign private issuer under the applicable corporate governance requirements of the Sarbanes-Oxley Act, the rules adopted by the SEC and Nasdaq listing rules.

Accordingly, our shareholders will not have the same protections afforded to shareholders of companies that are subject to all of the corporate governance requirements of Nasdaq. For an overview of our corporate governance principles, see the section titled "Description of share capital and articles of association —Differences in corporate law."

Item 16H. Mine Safety Disclosure

Not applicable.

PART III

Item 17. Financial Statements.

We have elected to provide financial statements pursuant to Item 18.

Item 18. Financial Statements.

The financial statements are filed as part of this Annual Report beginning on page F-1.

Item 19. Exhibits.

List all exhibits filed as part of the registration statement or Annual Report, including exhibits incorporated by reference.

		Incorporation by Reference			
Exhibit Number	Description	Schedule/Form	File Number	Exhibit	File Date
1.1*	Articles of Association of Orchard Therapeutics plc				
2.1*	Deposit Agreement				
2.2*	Form of American Depositary Receipt (included in Exhibit 2.1)				
2.1†	Asset Purchase and License Agreement, by and among the registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Ltd., dated April 11, 2018 (schedules, exhibits, and similar supporting attachments are omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request).	Form F-1	333-227698	2.1	10/4/18
4.1	Investment and shareholders' agreement by and between the registrant and the shareholders named therein, dated August 2, 2018.	Form F-1	333-227698	10.1	10/4/18
4.2#	2016 Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan, as amended.	Form F-1	333-227698	10.2	10/4/18
4.3*#	2018 Share Option and Incentive Plan. (Note: This exhibit is filed to replace Exhibit 10.3 to our Form F-1/A filed October 23, 2018, which contained typographical errors.)				
4.4	Deed of Novation, by and among the registrant, Glaxo Group Limited, GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline S.p.A., Fondazione Telethon and Ospedale San Raffaele (in its own capacity and as successor in interest to Fondazione Centro San Raffaele Del Monte Tabor), dated April 5, 2018.	Form F-1	333-227698	10.4	10/4/18

4.5	Research and Development Collaboration and License Agreement, by and among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended.	Form F-1	333-227698	10.5	10/4/18
4.6#	Form of Deed of Indemnity between the registrant and each of its directors and executive officers.	Form F-1	333-227698	10.6	10/4/18
4.7	Lease Agreement, dated as of January 19, 2018, by and between the Registrant and New Connect Investments Limited.	Form F-1	333-227698	10.7	10/4/18
4.8†	License and Development Agreement, by and between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended.	Form F-1	333-227698	10.8	10/4/18
4.9†	License Agreement between UCL Business Plc, The Regents of the University of California and the registrant, dated February 6, 2016, as amended.	Form F-1	333-227698	10.9	10/4/18
4.10#	2018 Employee Share Purchase Plan.	Form F-1/A	333-227698	10.10	10/23/18
4.11	Director Nomination Agreement, dated as of October 18, 2018, by and between the registrant and Glaxo Group Limited.	Form F-1/A	333-227698	10.11	10/23/18
4.12*	Lease Agreement, dated as of December 11, 2018, by and between BPP Pacific Industrial CA Non-REIT Owner 2 LLC and Orchard Therapeutics North America				
4.13*	Letter of Blick Rothenberg Audit LLP, dated March 19, 2019 regarding changes in Registrant's certifying accountants				
8.1*	Subsidiaries of the registrant				
12.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
12.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
13.1+	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				

13.2+	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
15.1*	Consent of Independent Registered Public Accounting Firm
101.INS*	XBRL Instance Document
101.SCH*	XBRL Taxonomy Extension Schema Document
101.CAL*	XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	XBRL Taxonomy Extension Presentation Linkbase Document

* Filed herewith.

\+ Furnished herewith

† Confidential treatment has been requested for portions of this exhibit. These portions have been omitted from the registration statement and filed separately with the United States Securities and Exchange Commission.

\# Indicates a management contract or any compensatory plan, contract or arrangement.

SIGNATURES

The registrant hereby certifies that it meets all of the requirements for filing on Form 20-F and that it has duly caused and authorized the undersigned to sign this Annual Report on its behalf.

Orchard Therapeutics plc

Date: March 22, 2019

By: /s/ Mark Rothera

Mark Rothera
President and Chief Executive Officer

Index to the Financial Statements

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of Orchard Therapeutics plc

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Orchard Therapeutics plc and its subsidiaries (the "Company") as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, of convertible preferred shares and shareholders' equity, and of cash flows for each of the three years in the period ended December 31, 2018, 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, 2018 and 2017, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2018 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
Reading, United Kingdom
March 22, 2019

We have served as the Company's auditor since 2018.

Orchard Therapeutics plc
Consolidated Balance Sheets
(In thousands, except share and per share amounts)

	December 31, 2018	December 31, 2017
Assets		
Current assets:		
Cash	$ 335,844	$ 89,856
Trade and other receivables	2,153	1,247
Prepaid expenses and other current assets	6,935	2,247
Research and development tax credit receivable	10,585	871
Total current assets	355,517	94,221
Non-current assets:		
Property and equipment, net	5,476	2,713
Restricted cash	3,837	—
Other long-term assets	1,212	360
Total non-current assets	10,525	3,073
Total assets	$ 366,042	$ 97,294
Liabilities, convertible preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 18,125	$ 3,891
Accrued expenses and other current liabilities	29,780	6,864
Total current liabilities	47,905	10,755
Other long-term liabilities	6,799	134
Total liabilities	54,704	10,889
Commitments and contingencies *(Note 12)*		
Shareholders' equity:		
Convertible preferred shares, £0.00001 par value; 33,771,174 shares authorized as of December 31, 2017; 33,277,678 shares issued and outstanding as of December 31, 2017; aggregate liquidation preference of $139,954 as of December 31, 2017.	—	134,069
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 and £675,413 of shares at December 31, 2018 and 2017, respectively;85,865,557 and 8,927,121 shares issued and outstanding at December 31, 2018 and 2017, respectively.	10,924	1,145
Additional paid-in capital	587,490	6,808
Accumulated other comprehensive income	3,163	4,127
Accumulated deficit	(290,239)	(59,744)
Total shareholders' equity	311,338	86,405
Total liabilities, convertible preferred shares and shareholders' equity	$ 366,042	$ 97,294

The accompanying notes are an integral part of these consolidated financial statements..

Orchard Therapeutics plc
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)

	Year Ended December 31,		
	2018	2017	2016
Product sales, net	$ 2,076	$ —	$ —
Costs and operating expenses			
Cost of product sales	422	—	—
Research and development	205,319	32,527	16,206
Selling, general and administrative	31,366	5,985	2,997
Total costs and operating expenses	237,107	38,512	19,203
Loss from operations	(235,031)	(38,512)	(19,203)
Other income (expense):			
Interest income	1,116	—	3
Change in fair value of tranche obligations	—	—	289
Other income (expense)	4,390	(1,179)	(154)
Total other income (expense), net	5,506	(1,179)	138
Net loss before income tax	(229,525)	(39,691)	(19,065)
Income tax expense	(970)	(53)	(20)
Net loss attributable to ordinary shareholders	$ (230,495)	$ (39,744)	$ (19,085)
Other comprehensive (loss) income			
Foreign currency translation adjustment	(964)	4,398	(271)
Total comprehensive loss	$ (231,459)	$ (35,346)	$ (19,356)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (10.22)	$ (4.48)	$ (2.69)
Weighted average number of ordinary shares outstanding, basic and diluted	22,559,389	8,872,768	7,100,528

The accompanying notes are an integral part of these consolidated financial statements.

Orchard Therapeutics plc
Consolidated Statement of Convertible Preferred Shares and Shareholders' Equity
(In thousands, except share amounts)

	Convertible preferred shares		Convertible preferred shares		Ordinary shares					
	Shares	Amount	Shares	Amount	Shares	Amount	Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
Balance at December 31, 2015	**—**	**$ —**	**—**	**$ —**	**2,697,151**	**$ 343**	**$ —**	**$ —**	**$ (915)**	**$ (572)**
Issuance of convertible preferred shares, net of issuance costs	11,204,199	16,970	—	—	—	—	—	—	—	—
Conversion of ordinary shares to deferred shares	—	—	—	—	(80,030)	—		—	—	—
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	—	—	—	—	4,829,810	614	2,121	—	—	2,735
Foreign currency translation adjustment	—	—	—	—	—	—	—	(271)	—	(271)
Net loss	—	—	—	—	—	—	—	—	(19,085)	(19,085)
Balance at December 31, 2016	**11,204,199**	**$ 16,970**	**—**	**$ —**	**7,446,931**	**$ 957**	**$ 2,790**	**$ (271)**	**$ (20,000)**	**$ (16,524)**
Issuance of convertible preferred shares, net of issuance costs	14,693,207	66,981	—	—	—	—	—	—	—	—
Reclassification of convertible preferred shares from temporary equity to permanent equity	(25,897,406)	(83,951)	25,897,406	83,951	—	—	—	—	—	83,951
Issuance of convertible preferred shares, net of issuance costs	—	—	7,380,272	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	—	—	—	—	1,480,190	188	1,465	—	—	1,653
Foreign currency translation adjustment	—	—	—	—	—	—	—	4,398	—	4,398
Net loss	—	—	—	—	—	—	—	—	(39,744)	(39,744)
Balance at December 31, 2017	**—**	**$ —**	**33,277,678**	**$ 134,069**	**8,927,121**	**$ 1,145**	**$ 6,808**	**$ 4,127**	**$ (59,744)**	**$ 86,405**
Issuance of convertible preferred shares, net of issuance costs	—	—	26,891,222	$ 242,744	—	—	—	—	—	242,744
Share-based compensation expense	—	—	—	—		—	6,766	—	—	6,766
Exercise of share options	—	—	—	—	14,545	2	26	—	—	28
Ordinary shares issued as part of license agreements	—	—	—	—	651,419	83	1,302	—	—	1,385
Effect of corporate reorganization, including conversion of preferred shares to ordinary shares	—	—	(60,168,900)	(376,813)	60,168,900	7,647	369,166	—	—	—
Issuance of ordinary shares in initial public offering net of issuance costs of $4,200	—	—	—	—	16,103,572	2,047	203,422	—	—	205,469
Foreign currency translation adjustment	—	—	—	—	—	—	—	(964)	—	(964)
Net loss	—	—	—	—	—	—	—	—	(230,495)	(230,495)
Balance at December 31, 2018	**—**	**$ —**	**—**	**$ —**	**85,865,557**	**$ 10,924**	**$ 587,490**	**$ 3,163**	**$ (290,239)**	**$ 311,338**

The accompanying notes are an integral part of these consolidated financial statements.

Orchard Therapeutics plc
Consolidated Statements of Cash Flows
(In thousands, except share amounts)

	Year Ended December 31,		
	2018	**2017**	**2016**
Cash flows from operating activities			
Net loss	$ (230,495)	$ (39,744)	$ (19,085)
Adjustments to reconcile net loss to net cash used in operating activities:			
Depreciation expense	1,199	302	6
Share-based compensation	6,766	1,019	204
Amortization of provision on loss contract	(6,300)	—	—
Non-cash consideration for licenses and milestones	94,776	3,126	3,089
Change in fair value of tranche obligation liability	—	—	(289)
Changes in components of operating assets and liabilities:			
Trade and other receivables	(927)	(1,168)	—
Research and development tax credit receivable, prepaids and other assets	(15,946)	(2,737)	(639)
Accounts payable	14,848	1,930	666
Accrued expenses and other current liabilities	31,663	4,672	1,460
Other long-term liabilities	6,880	113	22
Net cash used in operating activities	$ (97,536)	$ (32,487)	$ (14,566)
Cash flows from investing activities			
Purchases of property and equipment	(4,032)	(1,559)	(190)
Net cash used in investing activities	$ (4,032)	$ (1,559)	$ (190)
Cash flows from financing activities			
Issuance of convertible preferred shares, net of issuance costs	149,367	115,696	18,034
Issuance of ADRs in initial public offering, net of issuance costs	205,469	—	—
Proceeds from share options	28	—	—
Net cash provided by financing activities	$ 354,864	$ 115,696	$ 18,034
Effect of exchange rate changes on cash	(3,471)	4,709	(751)
Net increase in cash and restricted cash	$ 249,825	$ 86,359	$ 2,527
Cash and restricted cash —beginning of year	89,856	3,497	970
Cash and restricted cash —end of year	$ 339,681	$ 89,856	$ 3,497
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	—	1,402	451
Property and equipment included in accrued expenses and accounts payable at period end	—	1,247	—
Convertible preferred shares issued for licenses	93,391	—	—

The accompanying notes are an integral part of these consolidated financial statements.

1. Nature of Business and Basis of Presentation

Orchard Therapeutics plc (the "Company"), 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 a public limited company incorporated pursuant to the laws of England and Wales. 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.

Pursuant to the corporate reorganization, all 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.

On November 1, 2018, our different classes of preferred shares and our ordinary shares were consolidated on a one-for-0.8003 basis. Following the share consolidation, each share was re-designated as an ordinary share on a one-for-one basis. Accordingly, all share and per share amounts for all periods presented in the consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the reverse stock split.

On November 2, 2018, the Company closed its initial public offering (IPO) of American Depositary Shares ("ADS") in which the Company sold an aggregate of 16,103,572 ADSs representing the same number of ordinary shares at a public offering price of $14.00 per ADS. Net proceeds were $205.5 million, after deducting underwriting discounts and commissions of $15.8 million and offering expenses of $4.2 million paid by the Company. As part of the corporate reorganization as described above, each ordinary share with a nominal value of £0.00001 was redenominated as an ordinary share with a nominal value of £0.10. Accordingly, equity accounts for all periods presented in the consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the effects of the redenomination of our ordinary shares.

Orchard Therapeutics plc is a continuation of Orchard Therapeutics Limited and its subsidiaries, and the corporate reorganization has been accounted for as a combination of entities under common control. The corporate reorganization has been given retrospective effect in these financial statements and such financial statements represent the financial statements of Orchard Therapeutics Limited for all periods prior to the corporate reorganization. In connection with the corporate reorganization, outstanding share option awards of Orchard Therapeutics Limited were exchanged for share awards and option grants of Orchard Therapeutics plc with identical restrictions.

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, 2018, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares and ADSs in the IPO. The Company has incurred recurring losses since its inception, including net losses of $230.5 million, $39.7 million, and $19.1 for the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018, the Company had an accumulated deficit of $290.2 million. The Company expects to continue to generate operating losses for the foreseeable future. The viability of the Company is dependent on its ability to raise additional capital to finance its operations. 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. The Company expects that its cash on hand as of December 31, 2018 of $335.8 million, will be sufficient to fund its operations and capital expenditure requirements through at least the next twelve months.

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America ("U.S. GAAP") and include the accounts of the Company and its wholly owned subsidiaries, Orchard Therapeutics (Europe) Limited, Orchard Therapeutics North America, and Orchard Therapeutics (Netherlands) B.V., after elimination of all intercompany accounts and transactions.

Research and development tax credit receivable as of December 31, 2017 previously included in prepaid and other current assets has been presented as a separate line item on the consolidated balance sheet to conform to current period presentation.

2. Summary of Significant Accounting Policies

Use of estimates

The preparation of consolidated financial statements in conformity with U.S. 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 research and development tax credit receivable, the Stimvelis loss provision, the fair values of ordinary and convertible preferred shares, the fair value of tranche obligations, share-based compensation and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Changes in estimates are recorded in the period in which they become known. Actual results could differ materially from those estimates.

Concentration of credit risk

The Company has no significant off-balance sheet risk, such as foreign currency contracts, options contracts, or other foreign hedging arrangements. Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash and other receivables. Periodically, the Company maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

Foreign currency translation

The reporting currency of the Company is the U.S. dollar. The Company has determined the functional currency of the parent company, Orchard Therapeutics plc, is U.S. dollars because it predominantly raises finance and expends cash in U.S. dollars. The functional currency of our subsidiary operations is the applicable local currency. Transactions in foreign currencies are translated into the functional currency of the subsidiary in which they occur at the foreign exchange rate in effect on at the date of the transaction. Monetary assets and liabilities denominated in foreign currencies at the balance sheet date are translated into the functional currency of the relevant subsidiary at the foreign exchange rate in effect on the balance sheet date. Non-monetary assets and liabilities denominated in foreign currencies that differ from the functional currency are translated into the functional currency at the exchange rates prevailing at the date of the transaction. The Company recorded a foreign currency transaction gain of $4.4 million and foreign currency transaction loss of $1.2 million and $0.2 million for the years ended December 31, 2018, 2017 and 2016, respectively, which is included in other income (expense) in the statements of operations and comprehensive loss.

The results of operations for subsidiaries, whose functional currency is not the U.S. dollar, are translated at an average rate for the period where this rate approximates to the foreign exchange rates ruling at the dates of the transactions and the balance sheet of these subsidiaries are translated at foreign exchange rates prevailing at the balance sheet date. Exchange differences arising from this translation of foreign operations are reported as an item of other comprehensive loss.

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 2018 and 2017, the Company did not have any cash equivalents.

Restricted Cash

Cash and cash equivalents that are restricted as to withdrawal or use under the terms of certain contractual agreements are recorded as Restricted cash on our consolidated balance sheet. The Company has entered into a lease transaction (Note 12) that requires a letter of credit of $3.0 million at December 31, 2018. The Company is also contractually required to maintain a cash collateral account associated with corporate credit card accounts in the amount of $0.9 million at December 31, 2018. The Company had no restricted cash at December 31, 2017. The Company includes the restricted cash balance in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the consolidated statements of cash flows.

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, 2018, 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 U.S. GAAP. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

- Level 1—Quoted prices in active markets for identical assets or liabilities.
- Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.
- Level 3—Unobservable inputs that are supported by little or no market activity that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

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 tranche obligations settled in 2017, and no such obligations existed in 2018.

The fair values of the tranche obligations are based on significant inputs not observable in the market, which represents a Level 3 measurement within the fair value hierarchy. The tranche obligations are valued as a forward contract, and the values are determined using a probability-weighted present value calculation. In determining the fair values of the tranche obligations, estimates and assumptions impacting fair value included the fair value of the Company's convertible preferred shares, risk-free interest rates, the probability and estimated timing of the tranche closings, expected dividend yield and expected volatility of the price of the underlying convertible preferred shares. The Company determines the per share fair value of the underlying convertible preferred shares using the option pricing model ("OPM"), which considers the preferred share price paid by investors, the time to liquidity and volatility. In the OPM, the timing of the liquidity event determines the assumed life in the Black-Scholes calculation. The Company estimates a time to liquidity taking into account the future tranche funding. If the future tranche is not expected to be funded, a liquidity event will be assumed to have occurred. If the tranche is expected to be funded, a longer-term liquidity event is assumed to have occurred. Volatility is estimated based on the daily trading histories of comparable public companies. The risk-free interest rate is determined by reference to the United States Treasury yield curve. The Company estimated a 0% dividend yield based on the expected dividend yield and the fact that it has never paid or declared a 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 three geographic regions: the United Kingdom, European Union, and United States. The Company had fixed assets of $1.7 million and $3.8 million located in the United Kingdom and United States, respectively, as of December 31, 2018, and $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. In addition, funding from research grants is recognized as an offset to

research and development expense on the basis of costs incurred on the research program. Royalties associated with our research grants will be accrued when they become probable.

Research contract costs and accruals

The Company has entered into various research and development-related contracts. These agreements are cancelable, and related costs are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies or clinical trials, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Share-based compensation

The Company measures share-based awards granted to employees and directors based on the fair value on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is the vesting period of the respective award. Forfeitures are accounted for as they occur.

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.

Valuation of Stock Options

The fair value of each option is estimated on the date of grant using the Black-Scholes option pricing model. Assumptions used in the option pricing model include the following:

Expected volatility. 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.

Expected term. The expected term of the Company's share options has been determined utilizing the "simplified method" for awards that qualify as "plain-vanilla" options.

Risk-free interest rate. 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. 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.

Fair value of ordinary shares. Options granted subsequent to the Company's IPO are issued at the fair market value of the Company's ADS at the date of grant as approved by the board.

Prior to the IPO, given the absence of an active market for the Company's ordinary shares, the board of directors, the members of which the Company believes have extensive business, finance, and venture capital experience, was required to estimate the fair value of the Company's ordinary share at the time of each grant of a share-based award. The board of directors determined the estimated fair value of the Company's equity instruments based on a number of objective and subjective factors, including

external market conditions affecting the biotechnology industry sector. The Company and the board of directors utilized various valuation methodologies in accordance with the framework of the American Institute of Certified Public Accountants' Technical Practice Aid, *Valuation of Privately-Held Company Equity Securities Issued as Compensation*, to estimate the fair value of its ordinary shares. Each valuation methodology includes estimates and assumptions that require the Company's judgment. These estimates and assumptions include a number of objective and subjective factors in determining the value of the Company's ordinary shares at each grant date, including the following factors: (1) prices paid for the Company's convertible preferred shares, which the Company had sold to outside investors in arm's-length transactions, and the rights, preferences, and privileges of the Company's convertible preferred shares and ordinary shares; (2) valuations performed by an independent valuation specialist; (3) the Company's stage of development; (4) the fact that the grants of share-based awards involved illiquid securities in a private company; and (5) the likelihood of achieving a liquidity event for the ordinary shares underlying the share-based awards, such as an IPO or sale of the Company, given prevailing market conditions.

Ordinary share valuations were prepared using the OPM to estimate the Company's enterprise value. The OPM treats ordinary and 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.

Valuation of RSUs

We estimate the fair value of our performance-based restricted stock unit ("RSUs") awards or components of RSU awards whose vesting is contingent upon market conditions, such as volume weighted-average price ("VWAP"), using the Monte-Carlo simulation model. The fair value of RSUs or components of RSU awards where vesting is contingent upon market conditions is amortized based upon the estimated derived service period. The fair value of RSUs or components of RSUs granted to our employees and directors is determined, where vesting is dependent on future services or regulatory or research and development milestones, based upon the quoted closing market price per share on the date of grant.

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, 2018, 2017 and 2016, other comprehensive loss included a loss of $1.0 million, a gain of $4.4 million, and a loss of $0.3 million and, respectively, related to foreign currency translation adjustments.

Strimvelis loss provision

As part of the GSK transaction, the Company is required to maintain commercial availability of Strimvelis in the European Union until such time that an alternative gene therapy is available (Note 9). 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 associated with the loss contract of $18.4 million. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with Strimvelis and the expected future net losses to be generated until such time as Strimvelis is no longer commercially available. The amortization of the provision is recorded as a credit to research and development expense. We have made an estimate of the expected future losses associated with Strimvelis and adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. As of December 31, 2018, the total Strimvelis loss provision liability was $10.3 million. During the year-ended December 31, 2018 the Company amortized $6.3 million as a credit to research and development expense. The effects of foreign currency translation for the year-ended December 31, 2018 reduced the liability by $1.7 million.

Research and development income tax credit

As a company that carries out extensive research and development activities, the Company seeks to benefit from one of two U.K. research and development tax relief programs, the Small and Medium-sized Enterprises R&D Tax Credit Program (“SME Program”) and the Research and Development Expenditure program (“RDEC Program”). Qualifying expenditures largely comprise employment costs for research staff, consumables and certain internal overhead costs incurred as part of research projects for which the Company does not receive income. Such credits are accounted for 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, 2018, 2017 and 2016. The Company has qualified under the more favorable SME regime for the year ended December 31, 2018.

The RDEC and SME 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 a 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 $10.2 million, $0.7 million, and $0.2 million for the years ended December 31, 2018, 2017, and 2016, respectively. As of December 31, 2018, and 2017, the Company’s tax incentive receivable from the United Kingdom government was $10.6 million and $0.9 million, respectively. The effects of foreign currency translation for the year-ended December 31, 2018 reduced the receivable by $0.5 million. 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, and is generally applicable to our operations in the United Kingdom and European Union. 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 associated with our U.K. subsidiary 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 substantively enacted tax rates in effect for the year in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company assesses the likelihood that its deferred tax assets will be recovered in the future and, to the extent the Company believes, based upon the weight of available evidence, that it is more likely than not that all or a portion of the deferred tax assets will not be realized, a valuation allowance is established through a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company is subject to corporation taxes in the United Kingdom and the United States. The calculation of the Company's tax provision involves the application of both United Kingdom or United States tax law and requires judgement and estimates.

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

Net product sales

During the year, the Company made its first sales of Strimvelis, which is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. Strimvelis sales are currently under a buy-and-bill model where the treatment center purchases and pays for the product and submits a claim to the payer. The Company evaluated the variable consideration under Accounting Standards Codification (ASC) 606, *Revenue from Contracts with Customers*, and there is currently no variable consideration included in the transaction price for Strimvelis.

The Company's net product sales represent total gross product sales of Strimvelis. All sales are recognized when control is transferred, which occurs upon the completion of the scheduled Strimvelis treatment. Transduction costs associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates that there is minimal risk of product return, including the risk of product expiration.

Net income (loss) per share

The Company follows the two-class method when computing net income (loss) per share as the Company has issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of ordinary and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to ordinary shareholders for the period to be allocated between ordinary and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed.

Basic net income (loss) per share attributable to ordinary shareholders is computed by dividing the net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period. Diluted net income (loss) attributable to ordinary shareholders is computed by adjusting net income (loss) attributable to ordinary shareholders to reallocate undistributed earnings based on the potential impact of dilutive securities. Diluted net income (loss) per share attributable to ordinary shareholders is computed by dividing the diluted net income (loss) attributable to ordinary shareholders by the weighted average number of ordinary shares outstanding for the period, including potential dilutive ordinary shares. For purpose of this calculation, outstanding options and convertible preferred shares are considered potential dilutive ordinary shares.

The Company's convertible preferred shares contractually entitle the holders of such shares to participate in dividends but do not contractually require the holders of such shares to participate in losses of the Company. Accordingly, in periods in which the Company reports a net loss attributable to ordinary shareholders, such losses are not allocated to such participating securities. In periods in which the Company reports a net loss attributable to ordinary shareholders, diluted net loss per share attributable to ordinary shareholders is the same as basic net loss per share attributable to ordinary shareholders, since dilutive ordinary shares are not assumed to have been issued if their effect is anti-dilutive.

The Company reported a net loss attributable to ordinary shareholders for the years ended December 31, 2018, 2017, and 2016.

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.

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 for 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 adopted ASU 2017-09 as of January 1, 2018. The adoption of ASU 2017-09 did not have a material impact on the Company's financial position, results of operations or cash flows.

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 the guidance to our analysis of arrangements entered into during the years ended during the year ended December 31, 2016 and subsequent reporting periods.

In November 2016, the FASB issued ASU No. 2016-18, *Statement of Cash Flows (Topic 230): Restricted Cash* ("ASU 2016-18"), which requires companies to include amounts generally described as restricted cash and restricted cash equivalents in cash and cash equivalents when reconciling beginning-of-period and end-of-period total amounts shown on the statement of cash flows. The Company adopted ASU 2016-18 for annual period beginning after December 15, 2017. Prior to the adoption of ASU 2016-18, the Company did not have material balances meeting the definition of restricted cash or restricted cash equivalents.

In August 2016, the FASB issued Accounting Standards Update No 2016-15, *Statement of Cash Flows (Topic 230)*: *Classification of Certain Cash Receipts and Cash Payments* ("ASU 2016-15") to clarify guidance on the classification of certain cash receipts and payments in the statement of cash flows. The Company adopted this guidance as of January 1, 2018. The adoption of ASU 2016-15 did not have a material impact on the Company's financial statements.

In October 2016, the FASB issued ASU No. 2016-16, *Income Taxes (Topic 740)*: *Intra-Entity Transfer of Assets Other than Inventory* ("ASU 2016-16"), which requires the recognition of the income tax consequences of an intra-entity transfer (sales) of an asset, other than inventory, when the transfer occurs. The standard is effective for the Company beginning January 1, 2018. The Company does not currently engage in sale transactions with its wholly owned subsidiaries. Adoption of this standard did not have a material impact on the Company's consolidated financial statements.

In March 2016, the FASB issued ASU No. 2016-09, *Compensation—Stock Compensation (Topic 718): Improvements to Employee Share-Based Payment Accounting* ("ASU 2016-09"). ASU 2016-09 addresses several aspects of the accounting for share-based payment transactions, including the income tax consequences, classification of awards as either equity or liabilities, an option to recognize gross share compensation expense with actual forfeitures recognized as they occur, and classification on the statement of cash flows. Certain of these changes are required to be applied retrospectively, while other changes are required to be applied prospectively. ASU 2016-09 is effective for public entities for annual periods beginning after December 15, 2016, and interim periods within those annual periods. For all other entities, the guidance is effective for annual periods beginning after December 15, 2017, and interim periods within annual periods beginning after December 15, 2018. Early adoption is permitted for any entity in any interim or annual period and an entity that elects early adoption must adopt all of the amendments in the same period. The Company early adopted ASU 2016-09 effective as of January 1, 2016. The adoption of ASU 2016-09 did not have a material impact on the Company's financial position, results of operations or cash flows.

In January 2016, the FASB issued ASU 2016-01, *Financial Instruments – Overall (Subtopic 825-10): Recognition and Measurement of Financial Assets and Financial Liabilities* ("ASU 2016-01"), which amended the guidance on the recognition and measurement of financial assets and financial liabilities. The new guidance requires that equity investments (except those accounted for under the equity method of accounting, or those that result in consolidation of the investee) are measured at fair value with changes in fair value recognized in net income. The guidance also requires the use of an exit price when measuring the fair value of financial instruments for disclosure purposes, eliminates the requirement to disclose the methods and significant assumptions used to estimate the fair value that is required to be disclosed for financial instruments measured at amortized cost and requires separate presentation of financial assets and financial liabilities by measurement category and form of financial asset. The guidance became effective for the fiscal year beginning January 1, 2018, including interim periods within that fiscal year. Adoption of ASU 2016-01 did not have a material impact on the Company's consolidated financial statements as the Company does not hold any equity securities.

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 as the company has recorded a full valuation allowance on deferred tax assets for the period ended December 31, 2016 and subsequent reporting periods.

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 U.S. GAAP. The standard's core principle is that a company will recognize revenue when it transfers promised goods or services to customers in an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods or services. The standard defines a five-step process to achieve this principle and will require companies to use more judgment and make more estimates than under the current guidance. The Company expects that these judgments and estimates will include identifying performance obligations in the customer contract, estimating the amount of variable consideration to include in the transaction price and allocating the transaction price to each separate performance obligation. ASU 2014-09 also requires additional disclosure about the nature, amount, timing and uncertainty of revenue and cash flows arising from customer contracts. In August 2015, the FASB issued

ASU 2015-14, *Revenue from Contracts with Customers (Topic 606): Deferral of the Effective Date*, which delays the effective date of ASU 2014-09 such that the standard is effective for public entities for annual period beginning after December 15, 2017, including interim periods within those fiscal years. For all other entities, the guidance is effective beginning after December 15, 2018, and interim periods within annual periods beginning after December 15, 2019. Early adoption of the standard is permitted for annual periods beginning after December 15, 2016, including interim periods within those fiscal years. The Company adopted these revenue standards on January 1, 2017. Prior to 2018, the Company had no sources of revenue. In 2018, the Company had its first sales of Strimvelis and have applied this guidance to our revenue recognition, and as such there was no impact from the adoption of ASC 606 in prior periods.

Recently issued accounting pronouncements not yet adopted

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 does not expect ASU 2017-11 to have a material impact on the Company's financial position.

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 the Company in its annual periods beginning after December 15, 2019. The Company is currently evaluating the impact that the adoption of ASU 2016-02 will have on its consolidated financial statements.

The Company has considered other recent accounting pronouncements and concluded that they are either not applicable to the business, or that the effect is not expected to be material to the financial statements as a result of future adoption.

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, 2018 or 2017.

The following table presents information about the Company's financial liabilities that have been measured at fair value on a recurring basis as of December 31, 2016 (there were no financial liabilities measured at fair value on a recurring basis as of December 31, 2018 or 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 closing, 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

The following table provides a summary of the changes in fair value of the tranche obligation liability measured at fair value on a recurring basis using significant unobservable inputs during the years ended December 31, 2016 and 2017 (in thousands):

	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. Revenue Recognition

The Company adopted the new accounting guidance under ASC606 regarding recognition of revenue from customers as of January 1, 2018. Prior to 2018, the Company had no revenue, and the adoption of this guidance resulted in no cumulative adjustment to the Company's consolidated financial statements.

The Company currently has one commercial-stage therapy, Strimvelis, for the treatment of ADA-SCID. During the year, the Company made its first sales of Strimvelis, which is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. Strimvelis sales are currently under a buy-and-bill model where the treatment center purchases and pays the Company for the product and submits a claim to the payer.

The Company's net product sales represent total gross product sales of Strimvelis, less any allowances based on contractual terms or the arrangement with the treatment center. All sales are recognized when control is transferred, which follows the Company's verification of a scheduled Strimvelis treatment. Transduction costs associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates that there is minimal risk of product return, including the risk of product expiration. The Company excludes from measurement of the transaction price all taxes assessed by a governmental authority that are both imposed concurrent with the specific revenue-producing transaction and collected by the Company from a customer.

Payment terms and conditions generally require payment for Strimvelis sales within 60 days of treatment. Strimvelis is currently distributed exclusively at the San Rafaelle Hospital, and there is currently no variable consideration included in the transaction price of Strimvelis.

5. Property and Equipment

Property and equipment consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Property and equipment:		
Lab equipment	$ 4,930	$ 2,708
Leasehold improvements	1,487	244
Furniture and fixtures	403	59
Office and IT equipment	152	12
Property and equipment	$ 6,972	3,023
Less: accumulated depreciation	(1,496)	(310)
Property and equipment, net	$ 5,476	$ 2,713

Depreciation expense for the years ended December 31, 2018 and 2017 was $1.2 million and $0.3 million, respectively.

6. Accrued Expenses and Other Liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2018	2017
	(in thousands)	
Accrued external research and development expenses	$ 12,738	$ 1,834
Accrued payroll and related expenses	7,372	2,090
Accrued professional fees	1,186	394
Accrued other	2,762	279
Strimvelis liability - current portion	4,170	—
Deferred UCLA reimbursement	—	2,267
Due to UCLA	1,552	—
Total accrued expenses and other current liabilities	$ 29,780	$ 6,864

7. Shareholders' Equity and Convertible Preferred Shares

Ordinary shares

As of December 31, 2018, each holder of ordinary shares is entitled to one vote per ordinary share and to receive dividends when and if such dividends are recommended by the board of directors and declared by the shareholders. As of December 31, 2018, the Company has not declared any dividends.

As of December 31, 2018, the Company had authority to allot ordinary shares up to a maximum nominal value of £13,023,851.50 with a nominal value of £0.10 per share.

As of December 31, 2017, 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. 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 Liquidation Preferences. Through December 31, 2017, no cash dividends have been declared or paid.

As of December 31, 2017, the Company had authority to allot ordinary shares up to a maximum nominal value of £675,413, with a nominal value of £0.00001 per share. The authority has taken into consideration the conversion of outstanding Convertible Preferred Shares of 33,277,678 as of December 31, 2017; 500,596 ordinary shares the Company committed to issue as part of its license and research agreements as of December 31, 2017; 4,153,196 for the exercise of outstanding share options, as of December 31, 2017; and 2,354,595 shares remaining available for future issuance under the 2016 Share Option Plan as of December 31, 2017.

Initial Public Offering and Corporate Reorganization

On November 2, 2018, the Company closed its IPO of ADSs. In the IPO, the Company sold an aggregate of 16,103,572 ADSs representing the same number of ordinary shares at a public offering price of $14.00 per ADS, including a partial exercise by the underwriters of their option to purchase additional ADSs. Net proceeds were $205.5 million, after deducting underwriting discounts, and commissions and offering expenses paid by the Company of $4.2 million.

Immediately prior to the completion of the IPO, all outstanding Convertible Preferred Shares of Orchard Therapeutics plc were converted into their respective class of preferred shares of Orchard Therapeutics plc on a one-for-0.8003 basis. All ordinary shares were consolidated on a one-for-0.8003 basis. Following completion of these steps, and immediately prior to the completion of the IPO, each share outstanding was re-designated as an ordinary share on a one-for-one basis. Accordingly, all share and per share amounts for all periods presented in the accompanying consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect this reverse split. In addition, all share options for all periods presented have been adjusted retroactively to reflect this reverse split.

Additionally, as part of the corporate reorganization associated with our IPO, each ordinary share with a nominal value of £0.00001 was redenominated as an ordinary share with a nominal value of £0.10. Accordingly, equity accounts for all periods presented in the consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect the effects of the redenomination of our ordinary shares.

Other ordinary share issuances

In November 2016, as amended in September 2018, the Company entered into a license and development agreement with Oxford BioMedica U.K. Limited (“Oxford BioMedica”). As consideration for the rights and licenses granted to Orchard under the license and development agreement, the Company issued 588,220 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 150,826 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. In August 2018, the terms of the arrangement were modified to extend milestone agreements under the plan, and the second milestone was met and the company issued an additional 150,826 shares. The shares issued in 2018 were recorded based on their fair value at the time the agreement was modified of $1.4 million. The amounts were recorded to research and development expense in the years ended December 31, 2018, 2017, and 2016, respectively.

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”), pursuant to which the Company issued nil, 1,224,094, and 3,441,290 ordinary shares in 2018, 2017 and 2016, 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 $1.7 million and $2.1 million were recorded to research and development expense for the years ended December 31, 2017 and 2016, respectively.

In 2016 and 2017, the Company entered into several license agreements with various academic and health care institutions to in-license certain intellectual property rights and know-how relevant to its programs. Pursuant to these agreements, the Company issued 800,380 and 256,096 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 $1.4 million and $0.5 million in 2017 and 2016, respectively.

As of December 31, 2018, and 2017, the Company had outstanding 85,865,557 and 8,927,121 ordinary shares, respectively.

Convertible preferred shares

As of December 31, 2018, there were no Convertible Preferred Shares outstanding due to our corporate reorganization and IPO. As of December 31, 2017, the Articles, as further amended and restated (the "Amended Articles"), authorized a total of 33,771,174 convertible preferred shares with a par value of £0.00001 per share, of which 16,806,299 shares have been designated as Series A convertible preferred shares and 16,964,875 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. In August 2018, the Company issued Series C convertible preferred shares, which were classified as permanent equity within shareholders' equity on the Company's consolidated balance sheets.

Preferred share financings

In February 2016, the Company issued 5,335,333 Series A convertible preferred shares at a price of £1.25 per share (the "Series A Original Issue Price") of which 4,811,937 Series A convertible preferred shares were issued for net proceeds of $8.5 million and 523,396 Series A convertible preferred shares were issued in settlement of the Notes.

In May 2016, the Company issued and sold 266,767 Series A convertible preferred shares at a price of £1.25 per share for net proceeds of $0.4 million.

In July 2016, the Company issued and sold 5,335,333 Series A convertible preferred shares at a price of £1.25 per share for net proceeds of $8.7 million.

In August 2016, the Company issued and sold 266,766 Series A convertible preferred shares at a price of £1.25 per share for net proceeds of $0.4 million.

In January 2017, the Company issued and sold 5,335,333 Series A convertible preferred shares at a price of £1.25 per share for net proceeds of $8.2 million.

In February 2017, the Company issued and sold 266,766 Series A convertible preferred shares at a price of £1.25 per share for net proceeds of $0.4 million.

In March 2017, the Company issued and sold 5,805,376 Series B convertible preferred shares at a price of £5.022 per share (the "Series B Original Issue Price") for net proceeds of $36.0 million.

In August 2017, the Company issued and sold 3,285,731 Series B convertible preferred shares at a price of £5.022 per share for net proceeds of $21.0 million.

In October 2017, the Company issued and sold 4,655,985 Series B convertible preferred shares at a price of £5.022 per share for net proceeds of $30.8 million.

In December 2017, the Company issued and sold 2,724,288 Series B convertible preferred shares at a price of £5.022 per share for net proceeds of $18.3 million.

In December 2017, the Company received proceeds of $1.0 million for 150,706 Series B convertible preferred shares, which were subsequently issued in January 2018.

In August 2018, the Company issued and sold 13,942,474 Series C convertible preferred shares at a price of $10.76 per share for net proceeds of $147.1 million.

As of December 31, 2018, there were no Convertible Preferred Shares outstanding due to our corporate reorganization and IPO. As of December 31, 2017, 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	16,806,298	16,806,298	$ 26,994	$ 28,337	16,806,298
Series B convertible preferred shares	16,964,876	16,471,380	107,075	111,617	16,471,380
	33,771,174	33,277,678	$ 134,069	$ 139,954	33,277,678

(a) Amounts were translated into United States dollars using the spot rate as of December 31, 2017.

There were no Convertible Preferred Shares outstanding as of December 31, 2018. 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 preferred 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 and Series B preferred share was 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 or Series B Original Issue Price by the respective Series A or 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, 2017, each Preferred Share was convertible into one ordinary share.

As set forth in the Amended Articles, the Series A and B Conversion Prices were 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 would 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 £6.0262, 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 were 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 ranked 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 were entitled to receive any declared but unpaid dividend, in the order of the priority set out in Liquidation Preference above, on each outstanding Series A convertible preferred share and Series B convertible preferred share. No dividends were declared or paid during the year ended December 31, 2017 and 2018.

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.

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 £1.25 from the distribution of assets on a liquidation or return of capital event.

In 2016, the Company converted 80,030 ordinary shares of an investor to deferred shares. In March 2017, the Company repurchased 80,030 deferred shares at £0.00001 per share and simultaneously cancelled them.

There were no deferred shares outstanding as of December 31, 2017 and 2018.

8. Share-based Compensation

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 provided for the Company to grant incentive and non-qualified options to officers, directors, consultants, and advisors to purchase the Company's ordinary shares prior to the IPO. The board of directors has determined not to make any further awards under the 2016 plan following the Company's IPO.

In October 2018, as part of the Company's reorganization and IPO, the Company adopted the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"). The 2018 Plan provides for grants in the form of incentive and non-qualified options, share appreciation rights, restricted shares, and restricted share units. The Company issues new ordinary shares upon exercise of share options. The Company has initially reserved 4,254,741 ordinary shares, or the initial limit, for the issuance of awards under the 2018 Plan. As of December 31, 2018, 3,953,726 shares remained available for future grant under the plan. The number of ordinary shares reserved for issuance will automatically increase each January 1, beginning 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 the board of directors.

In October 2018, the Company adopted the 2018 Employee Share Purchase Plan (the "ESPP") under which eligible employees may contribute up to 15% of their base compensation toward bi-annual purchases of the Company's ordinary shares. The ESPP initially reserved and authorized the issuance of up to a total of 850,948 ordinary shares to participating employees. The number of ordinary shares reserved for issuance will automatically increase 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 purchase price for each ordinary share is the lesser of 85% of the market price on the first business day or last business day of the offering period. Share-based compensation expense related to this plan was $0.1 million for the year ended December 31, 2018.

Prior to the Company's IPO, the Company typically granted 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. After the IPO, options are typically granted at exercise prices equal to the fair value of the Company's ordinary shares on the grant date. The vesting period is determined by the board of directors, which is generally four years. An option's maximum term is ten years.

Option valuation

The assumptions used in the Black-Scholes option pricing model to determine the fair value of the share options granted to employees, non-employees, and directors during the year ended December 31, 2018, 2017, and 2016 were as follows:

	Year Ended December 31,		
	2018	2017	2016
Risk-free interest rate% - %	2.66% - 3.03%	1.52% - 2.30%	1.52% - 2.40%
Expected term (in years)	5.00 - 6.08	6.08	6.08 - 9.75
Expected volatility% - %	64.27 - 68.58%	77.80% - 80.00%	77.80% -79.70%
Expected dividend rate%	0.00%	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 significant trading history for its ordinary shares.

Risk-Free Interest Rate: The Company based the risk-free interest rate over the expected term of the options 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: Prior to the IPO, 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. Subsequent to the IPO, the Company determined the fair value of the underlying ordinary shares based on the close price of our ordinary shares on the grant date.

Options

The following table summarizes option activity under the plans for the year ended December 31, 2018:

	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	4,153,196	$ 1.20	9.28	$ 10,483
Granted	6,303,465	4.23		
Exercised	(14,547)	1.96		
Cancelled	(238,682)	2.55		
Options outstanding at December 31, 2018	10,203,432	3.04	8.97	129,551
Vested as of December 31, 2018	2,022,399	1.11	8.20	29,568

The weighted average exercise price of options granted to United Kingdom employees in 2018 was the nominal value of the underlying shares. The weighted average exercise price of options granted to United States employees in 2018 was $5.74.

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. During 2018, the total intrinsic value of share options exercised was not material. There were no share option exercises in 2017 or 2016.

The weighted average grant date fair value of the options granted during the years ended December 31, 2018, 2017, and 2016 was $5.23 per share, $2.70 per share and $0.92 per share, respectively.

Restricted Share Units

In November 2018, the Company issued performance-based restricted share units ("RSUs") to our Chief Executive Officer covering a maximum of 219,922 ordinary shares. The performance-based RSUs will vest, if at all, based upon the Company achieving three specific regulatory and research and development milestones, or one market condition based upon the volume weighted-average price ("VWAP") of the Company's ADSs for a certain period. Upon achievement of any of the aforementioned milestones, one third of the RSU's will vest, and the award will become fully vested upon achievement of three of the four performance conditions.

The maximum aggregate total fair value of the performance-based RSUs is $4.5 million. The fair value associated with the shares that could vest based on the market-based condition is being recognized as expense over the derived service period of 1.3 years. The fair value associated with the performance-based conditions will be recognized when achievement of the milestones becomes probable, if at all. The Company determined that, as of December 31, 2018, none of the regulatory and research development milestones were deemed probable.

The following table summarizes RSU award activity for the year ended December 31, 2018:

	Shares	Weighted Average Fair Value
Unvested at December 31, 2017	—	$ —
Granted	219,922	15.48
Vested	—	—
Forfeited	—	—
Unvested at December 31, 2018	219,922	15.48

The amount of compensation cost recognized for the years ended December 31, 2018 and 2017 for the market condition associated with the performance-based RSUs was $0.1 million and nil, respectively.

Share-based compensation

Share-based compensation expense related to share options, restricted share unit awards, and the employee stock purchase plan was classified in the consolidated statements of operations and comprehensive loss as follows:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Research and development	$ 2,740	$ 615	$ 181
Selling, general and administrative	4,026	404	23
Total	$ 6,766	$ 1,019	$ 204

The Company had 8,181,033 unvested options outstanding as of December 31, 2018. As of December 31, 2018, total unrecognized compensation cost related to unvested stock option grants was approximately $33.3 million. This amount is expected to be recognized over a weighted average period of approximately 2.96 years. As of December 31, 2018, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $4.5 million, depending upon achievement of the milestones.

9. 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 three additional earlier-stage development programs, which such option rights have lapsed as of the date of this Annual Report.

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 12,455,252 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 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 Series B-2 convertible preferred shares were converted to ordinary shares as part of our IPO in November 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 GSK. For accounting purposes, as of December 31, 2018, the Company does not consider the attainment of a PRV from the United States Food and Drug Administration to be probable.

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 associated with the loss contract of £12.9 million ($18.4 million at the acquisition date) associated with the loss expected due to this obligation. This liability is being amortized over the remaining period of expected sales of Strimvelis as a credit to research and development expenses (Note 2). During the period ended December 31, 2018, the Company amortized $6.3 million as a credit to research and development expenses associated with the loss provision. The effects of foreign currency translation for the year-ended December 31, 2018 reduced the liability by $1.7 million. The balance of the liability as of December 31, 2018 was $10.3 million. 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 (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 a 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 in milestone payments upon achievement of certain sales milestones applicable to GSK. The Company's royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. The Company's royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048. Other than Strimvelis, these royalty and milestone payments were not determined to be probable and estimable at the date of the acquisition and are not included as part of consideration.

The Company and GSK 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 expired 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, as well as options over three additional earlier-stage development programs. The Company's options under the agreement with Telethon-OSR with respect to the earlier-stage programs have lapsed.

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. The Company may pay up to and aggregate of approximately €31.0 million in 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 4,665,384 ordinary shares to UCLB, of which 1,224,094, and 3,441,290 ordinary shares were issued in 2017 and 2016, 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. 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 $0.2 million, $1.8 million, and $4.6 million of research and development costs in respect of UCLB, which comprise the upfront payments, issuance of ordinary shares and payments for clinical data, for the years ended December 31, 2018, 2017, and 2016, respectively.

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of $0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company is obligated to make payments to the parties of up to an aggregate of $38.9 million upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

In connection with the UCLB/UCLA License Agreement, in February 2016 the Company sold an aggregate of 800,298 Series A convertible preferred shares at a price of £1.25 per share (Note 14).

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, and amended in September 2018, 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 588,220 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 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and third milestones were achieved, and the Company issued 150,826 ordinary shares. If future milestones are met, the Company may become obligated to issue more 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 Company recorded $1.4 million upon achievement of the second and third development milestones in 2018. The expense recognized in 2016 and 2017 was determined based on the ordinary shares' fair value as of the time the agreement was executed. The expense recognized in 2018 was determined based on the ordinary shares' fair value as of the time the agreement was modified in September 2018.

The Company may also pay low single-digit percentage royalties on net sales of collaborated product generated under the Oxford BioMedica Agreement.

UCLA/CIRM 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 original amount of total reimbursement the Company could have received under the UCLA Research Agreement was $10.4 million. Through June 30, 2018, the Company received and recognized $7.3 million from this agreement. In July 2018, a transfer of the sponsorship took place and the Company became the awardee under the program funded by CIRM, and the Company received an award that superseded the previous award noted above. The total reimbursement the Company may receive under the new award is $8.5 million, of which we may be obligated to reimburse UCLA for up to $5.5 million for research activities upon achievement of certain milestones. Reimbursement may be received from CIRM during the period from January 2017 to December 2021. Under the terms of the CIRM grants, the Company is obligated to pay royalties based on a low single digit royalty percentage on net sales of CIRM-funded product candidates or CIRM-funded technology. The Company has the option to decline any and all amounts awarded by CIRM. As an alternative to revenue sharing, the Company has the option to elect to convert the award to a loan, payable within 10 days of election. No such election has been made as of the date of this Annual Report. The reimbursements are 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. The Company accrues the sales-based royalties associated with CIRM-funded products when payment becomes probable. To date, no royalties have been accrued.

For the year ended December 31, 2018 and 2017, the Company recorded $3.0 million and $5.0 million as a reduction of research and development expenses related to the UCLA Research Agreement. As of December 31, 2018, the Company recorded $1.6 million in accrued expenses for amounts which it is obligated to reimburse to UCLA under the July 2018 grant. 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.

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 1,030,786 and 375,380 ordinary shares, respectively. The Company made cash payments of nil, $2.7 million and $0.4 million 2018, 2017, and 2016, 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 nil, $1.4 million and $0.5 million in 2018, 2017 and 2016, 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 percentage royalties on net sales of products and services associated with the in-licensed technology.

10. Income Taxes

The components of loss from operations before income taxes for the years ended December 31, 2018, 2017, and 2016 are as follows:

	December 31,		
	2018	2017	2016
	(in thousands)		
U.K.	(230,543)	(39,422)	(19,105)
Non-U.K.	1,018	(269)	40
Loss before taxes	$ (229,525)	$ (39,691)	$ (19,065)

The provision for income taxes for the years ended December 31, 2018, 2017, and 2016 was computed at the United Kingdom statutory income tax rate. The income tax provision for the years then ended comprised:

	December 31,		
	2018	2017	2016
	(in thousands)		
Current provision expense			
Federal—United States	$ 607	$ —	$ —
State—United States	444	16	17
United Kingdom	—	—	—
Total current provision expense	1,051	16	17
Deferred provision expense			
Federal—United States	(31)	—	—
State—United States	(50)	37	3
United Kingdom	—	—	—
Total deferred provision expense	(81)	37	3
Total provision for income taxes	$ 970	$ 53	$ 20

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,		
	2018	2017	2016
	(in thousands)		
Income taxes at United Kingdom statutory rate	$ (43,526)	$ (7,640)	$ (3,831)
State income taxes	370	41	14
Permanent differences	293	115	75
Tax credits	—	(286)	(99)
Foreign rate differential	20	(40)	6
Change in valuation allowance	43,562	7,827	3,855
Impact of United States tax reform	159	36	—
Other	92	—	—
Total provision expense for income taxes	$ 970	$ 53	$ 20

Significant components of the Company's deferred tax assets and liabilities as of December 31, 2018 and 2017 consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Deferred tax assets		
Net operating loss carryforwards	$ 29,436	$ 9,483
Research and development credits	—	356
Share-based compensation	1,297	147
Amortization	19,451	2,156
Accruals	184	28
Other	1,946	—
Total deferred tax assets	$ 52,314	$ 12,170
Valuation allowance	(51,281)	(11,882)
Net deferred tax assets	$ 1,033	$ 288
Deferred tax liabilities		
Depreciation	$ (991)	$ (328)
Other non-current liabilities (net deferred tax assets and liabilities)	$ 42	$ (40)

As of December 31, 2018, the Company had approximately $155.2 million of United Kingdom net operating loss carryforwards.

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).

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 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 Kingdom deferred tax assets. Accordingly, a full valuation allowance has been established against these net deferred tax assets as of December 31, 2018 and 2017, respectively. The Company reevaluates the positive and negative evidence at each reporting period.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2018, 2017, and 2016 related primarily to the increase in net operating loss carryforwards and were as follows:

	December 31,		
	2018	2017	2016
	(in thousands)		
Valuation allowance as of beginning of year	$ (11,882)	$ (3,503)	—
Decreases recorded as benefit to income tax provision	604	—	—
Increases recorded to income tax provision	(44,166)	(7,827)	(3,855)
Effect of foreign currency translation	4,163	(552)	352
Valuation allowance as of end of year	$ (51,281)	$ (11,882)	$ (3,503)

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending tax examinations. The Company's tax years are still open under statute from December 31, 2015, to the present. The resolution of tax matters is not expected to have a material effect on the Company's consolidated financial statements.

11. Net Loss Per Share

The following table sets forth the computation of basic and diluted net loss per share:

	Year Ended December 31		
	2018	2017	2016
	(In thousands, except per share and share amounts)		
Net loss	$ (230,495)	$ (39,744)	$ (19,085)
Net loss attributable to ordinary shareholders	$ (230,495)	$ (39,744)	$ (19,085)
Weighted average ordinary shares outstanding, basic and diluted	22,559,389	8,872,768	7,100,528
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (10.22)	$ (4.48)	$ (2.69)

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, presented based on amounts outstanding at each period end, 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,		
	2018	2017	2016
Convertible preferred shares	—	33,277,678	11,204,199
Share options	9,179,247	3,612,288	1,809,442
Unvested performance-based restricted share units	219,922	—	—
	9,399,169	36,889,966	13,013,641

12. Commitments and Contingencies

Operating lease agreements

In October 2016, the Company entered into a lease agreement for laboratory space in Foster City, California, United States. The lease has a term of 5 years and expires in October 2021. The annual rental expense approximates $0.2 million. The Company was provided with one month of free rent.

In November 2017, the Company entered into a lease agreement for laboratory space in Menlo Park, California, United States. The lease expires in November 2020. The annual rental expense approximates $0.8 million. The Company was provided with one month of free rent.

In January 2018, the Company entered into a lease agreement for additional office space in London, United Kingdom. The lease has a term of five years and terminates in January 2023. The annual rental expense approximates $0.8 million.

In March 2018, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental expense approximates $0.3 million.

In December 2018, the Company leased additional office space in London, United Kingdom. The lease commenced on December 7, 2018 and terminates on January 7, 2023. The annual rental expense approximates $0.1 million.

Fremont lease agreement

In December 2018, the Company leased manufacturing and office space in Fremont, California, which terminates in May 2030. The annual rent expense approximates $2.4 million. The Company was provided with 8 months of free rent. Subject to the terms of the lease agreement, the Company executed a $3.0 million letter of credit upon signing the lease, which may be reduced by 25% subject to reduction requirements specified therein. This amount is classified as restricted cash on the consolidated balance sheet.

The Company intends to perform non-normal tenant improvements to the property to customize the facility to suit the Company's unique manufacturing needs. The Company is responsible for paying directly the costs associated with the construction project and as such the Company will be deemed for accounting purposes only to be the owner of the construction project, even though it is not the legal owner. As of December 31, 2018, no construction has begun related to the facility. The lease provides for approximately $5.0 million in tenant improvement allowances to be reimbursed to the Company by the landlord, which will be amortized into rental expense over the term of the lease.

Upon the start of construction, the Company is required to deposit $10.0 million in an escrow account. Subject to the terms of the lease and reduction provisions, this amount may be decreased to nil over time. As of December 31, 2018, no construction has begun, and the Company has no funds deposited in the escrow account.

Future minimum lease payments

The following table summarizes the future minimum lease payments due under all operating leases as of December 31, 2018:

Due in:	**(in thousands)**
2019	$ 3,303
2020	4,910
2021	4,135
2022	3,921
2023	2,844
Thereafter	20,386
Total	$ 39,499

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 $2.4 million, $0.7 million and $0.2 million for the years ended December 31, 2018, 2017 and 2016, respectively.

Other funding commitments

The Company has entered into several license agreements (Note 9). In connection with these agreements the Company is required to make milestone payments and annual license maintenance payments not met at December 31, 2018 and 2017 or royalties on future sales of specified products. The Company determined that no milestone payments that have not already been accrued were probable as of December 31, 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 December 31, 2018, and December 31, 2017, there was $0.8 million and $nil included within prepayments relates to prepaid instalments against these minimum commitments. The Company is committed to make further payments totaling $10.1 million between January 2019 and March 2021.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

13. 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 $0.6 million, $0.2 million, and $31,000 in matching contributions for the years ended December 31, 2018, 2017 and 2016, respectively.

14. Related-party Transactions

UCLB

Subsequent to our Series C preferred share financing in August 2018, UCLB is no longer a principal shareholder, and is no longer considered an affiliated entity of the Company as of December 31, 2018.

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 800,298 Series A shares (Note 9). At the same time, UCLB also entered into the UCLB/UCLA License Agreement (Note 9), 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 2018, 2017, and 2016 the Company incurred $0.2 million, $0.2 million, and $0.4 million of consulting fees, with an affiliate of UCLB, respectively.

GSK

In April 2018, the Company entered into 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-OSR (See Note 9). As consideration for the license the Company paid an upfront fee of $14.1 million, incurred an inventory purchase liability of $6.9 million, and issued 12,455,252 Series B convertible preferred shares valued at $93.4 million. Additionally, as part of the GSK agreement, the Company obtained, and is responsible for maintaining the commercial availability of Strimvelis. The Company recorded a loss provision of $18.4 million associated with the contract, as the costs to maintain Strimvelis are expected to significantly exceed revenues.

The issuance of the convertible preferred shares made GSK a principal shareholder in the Company.

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 outlined several activities that the Company 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 expired in December 2018. In 2018 the Company paid $14.0 million in pass-through research and development and royalty costs with GSK associated with the TSA. As of December 31, 2018, the company had $6.0 million in accrued expenses and accounts payable associated with the GSK TSA.

Convertible preferred shares

In February 2016, entities affiliated with F-Prime Capital purchased 16,006,000 Series A convertible preferred shares.

In December 2017, entities affiliated with F-Prime Capital and Scottish Investment Trust purchased 2,400,900 and 3,201,200 Series B convertible preferred shares.

In December 2017, the Company sold to its Chief Executive Officer, Chief Medical Officer and Senior Vice President of Business Development and Alliance Management 39,825, 9,955 and 3,982 Series B convertible preferred shares.

In August 2018, entities affiliated with Deerfield Management Company and Scottish Mortgage Investment Trust purchased 4,647,500 and 697,125 Series C convertible preferred shares at a price of

In August 2018, the Company sold to its Chief Executive Officer, Chief Financial Officer, and various members of its board of directors 24,979, 9,294, and 90,158 Series C convertible preferred shares.

All convertible preferred shares were converted to ordinary shares as part of the Company's IPO.

Initial public offering

In November 2018, entities affiliated with Deerfield Management Company, RA Capital Management LLC, Temasek Holdings (Private) Limited, and Scottish Mortgage Investment Trust purchased 3,376,100, 2,057,432, 1,000,000 and 925,000 ADSs, respectively, in the IPO. Subsequent to the IPO and as of December 31, 2018, each of these entities holds more than 5% of the Company's share capital.

In November 2018, our Chief Executive Officer, Chief Financial Officer, and members of the board of directors purchased 18,500, 5,000, and 13,000 ADRs, respectively, in the IPO.

15. Subsequent Events

Grants of share options and performance-based restricted share units under the 2018 Plan

On January 2, 2019, the Company granted options to employees for the purchase of an aggregate of 117,280 ordinary shares, at a weighted average exercise price of $14.98 per share. The aggregate grant-date fair value of these options was $1.1 million, which will be recognized as share-based compensation expense over the vesting period of four years.

On January 16, 2019, the Company granted options to senior management and employees for the purchase of an aggregate of 2,470,423 ordinary shares, at a weighted average exercise price of $12.54 per share. The aggregate grant-date fair value of these options was $19.8 million, which will be recognized as share-based compensation expense over the vesting period of approximately four years. The Company also granted performance-based RSUs to certain of its executives covering a maximum of 219,500 ordinary shares. These performance-based RSUs will vest, if at all, based upon attainment of certain regulatory and market-based milestones, but must vest by December 31, 2021 or else be forfeited. The maximum aggregate total fair value of these RSUs that could be recognized over this period is $3.3 million.

On February 1, 2019, the Company granted options to employees for the purchase of an aggregate of 95,800 ordinary shares, at a weighted averaged exercise price of $12.86 per share. The aggregate grant-date fair value of these options was $0.8 million, which will be recognized as share-based compensation expense over the vesting period of four years.

On March 1, 2019, the Company granted options to employees for the purchase of an aggregate of 24,700 ordinary shares, at a weighted averaged exercise price of $16.89 per share. The aggregate grant-date fair value of these options was $0.3 million, which will be recognized as share-based compensation expense over the vesting period of four years.

On March 13, 2019, the Company granted performance-based RSUs to certain members of its senior management covering 108,000 ordinary shares. These performance-based RSUs will vest, if at all, based upon attainment of certain regulatory and market-based milestones, but must vest by December 31, 2021 or else be forfeited. The maximum aggregate total fair value of these RSUs that could be recognized over this period is estimated to be $1.9 million.

Dated 2 November 2018

The Companies Act 2006
Public Company Limited by shares

ARTICLES OF ASSOCIATION

of

ORCHARD THERAPEUTICS PLC

TABLE OF CONTENTS

Company number: 11494381

NEW

ARTICLES OF ASSOCIATION

of

ORCHARD THERAPEUTICS PLC (the "Company")

1 **Defined terms**

1.1 No regulations or articles set out in any statute, or in any statutory instrument or other subordinate legislation made under any statute, concerning companies (including the regulations in the Companies (Model Articles) Regulations 2008 (SI 2008/3229)) shall apply as the articles of the Company. The following shall be the articles of association of the Company.

2 **Interpretation**

2.1 In these Articles, the following words and expressions shall have the meanings set out below:

"**Act**" means the Companies Act 2006

"**address**" includes any number or address used for the purposes of sending or receiving documents or information by electronic means

"**Articles**" means these articles of association as altered from time to time and Article shall be construed accordingly

"**Board**" means the board of Directors for the time being of the Company or the Directors present or deemed to be present at a duly convened quorate meeting of the Directors

"**certificated shares**" a share which is not an uncertificated share and references in these Articles to a share being held in certificated form shall be construed accordingly

"**clear days**" in relation to a period of notice means that period excluding the day when the notice is served or deemed to be served and the day for which it is given or on which it is to take effect

"**Companies Acts**" means the Act, the Companies Act 1985 and, where the context requires, every other statute from time to time in force concerning companies and affecting the Company

"**Deferred Shares**" has the meaning given to it in Article 4

"**Director**" means a director for the time being of the Company

"**FSMA**" means the Financial Services and Markets Act 2000

"**electronic form**" has the meaning given to it in section 1168 of the Act

"**electronic means**" has the meaning given to it in section 1168 of the Act

“**Listing**” means the listing of the Company's Ordinary Shares (in the form of American depositary shares) on NASDAQ

"**member**" means a member of the Company, or where the context requires, a member of the Board or of any committee

"**NASDAQ**" means The NASDAQ Stock Market LLC

"**NASDAQ Rules**" means the rules of NASDAQ

"**Office**” means the registered office from time to time of the Company

"**Operator**" means Euroclear UK and Ireland Limited or such other person as may for the time being be approved by HM Treasury as Operator under the uncertificated securities rules

"**Ordinary Shares**" has the meaning given to it in Article 4

"**paid up**" means paid up or credited as paid up

"**participating class**" means a class of shares title to which is permitted by the Operator to be transferred by means of a relevant system.

"**Register**" means the register of members of the Company to be maintained under the Act or as the case may be any overseas branch register maintained under Article 117

"**relevant system**" means a computer-based system which allows units of securities without written instruments to be transferred and endorsed pursuant to the uncertificated securities rules

"**Seal**" means the common seal of the Company or, where the context allows, any official seal kept by the Company under section 50 of the Act

"**Secretary**" means the secretary of Company for the time being;

"**Share Warrant**" means a warrant to bearer issued by the Company in respect of its shares

"**uncertificated securities rules**" means any provision of the Companies Acts relating to the holding, evidencing of title to, or transfer of uncertificated shares and any legislation, rules or other arrangements made under or by virtue of such provision (including the Uncertificated Securities Regulations 2001 as amended or replaced from time to time and any subordinate legislation or rules made under them for them time being in force)

"**uncertificated share**" means a share of a class which is at the relevant time a participating class, title to which is recorded on the Register as being held in uncertificated form and references in these Articles to a share being held in uncertificated form shall be construed accordingly

2.2 Headings are used for convenience only and shall not affect the construction or interpretation of these Articles.

2.3 A **person** includes a corporate and an unincorporated body (whether or not having separate legal personality).

2.4 Words in the singular shall include the plural and vice versa.

2.5 A reference to one gender shall include a reference to the other gender.

2.6 A reference to a statute or statutory provision is a reference to it as it is in force for the time being, taking account of any amendment, extension, or re-enactment and includes any subordinate legislation for the time being in force made under it.

2.7 Any words or expressions defined in the Companies Acts in force when these Articles or any part of these Articles are adopted shall (if not inconsistent with the subject or context in which they appear) have the same meaning in these Articles or that part, save that the word **company** shall include any body corporate.

2.8 A reference to a document **being signed** or to **signature** includes references to its being executed under hand or under seal or by any other method and, in the case of a communication in electronic form, such references are to its being authenticated as specified by the Companies Acts.

2.9 A reference to **writing** or **written** includes references to any method of representing or reproducing words in a legible and non-transitory form whether sent or supplied in electronic form or otherwise.

2.10 A reference to documents or information **being sent or supplied by or to** a company (including the Company) shall be construed in accordance with section 1148(3) of the Act.

2.11 A reference to a **meeting** shall not be taken as requiring more than one person to be present if any quorum requirement can be satisfied by one person.

2.12 If any Article (or part thereof) is or becomes inconsistent with any laws or regulations of any country to which affairs of the Company are subject such laws or regulations shall prevail and the relevant Article (or part thereof) shall be construed accordingly.

3 **Form of Resolution**

Subject to the Companies Acts, where anything can be done by passing an ordinary resolution, this can also be done by passing a special resolution.

4 **Capital**

The capital of the Company is divided into an unlimited number of ordinary shares of £0.10 pence each ("**Ordinary Shares**") and an unlimited number of deferred shares of £4.89687 pence each ("**Deferred Shares**") conferring on the holders the rights and being subject to the restrictions set out in this Article 10.

5 **Limited Liability**

The liability of the members of the Company is limited to the amount, if any, unpaid on the shares in the Company held by them.

6 **Change of Name**

The Company may change its name by resolution of the Board.

7 **Power to Attach Rights to Shares**

Subject to the Companies Acts and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the Company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the Board may determine.

8 **Allotment of Shares and Pre-Emption**

8.1 Subject to the Companies Acts, these Articles and to any relevant authority of the Company in general meeting required by the Act, the Board may offer, allot (with or without conferring rights of renunciation), grant options over or otherwise deal with or dispose of shares or grant rights to subscribe for or convert any security into shares to such persons, at such times and upon such terms as the Board may decide. No share may be issued at a discount.

8.2 The Board may, at any time after the allotment of any share but before any person has been entered in the Register, recognise a renunciation by the allottee in favour of some other person and accord to the allottee of a share a right to effect such renunciation and/or allow the rights to be represented to be one or more participating securities, in each case upon and subject to such terms and conditions as the Board may think fit to impose.

8.3 Under and in accordance with section 551 of the Act, the Directors shall be generally and unconditionally authorised to exercise for each prescribed period all the powers of the Company to allot shares up to an aggregate nominal amount equal to the Section 551 Amount (as defined below).

8.4 Under and within the terms of the said authority or otherwise in accordance with section 570 of the Act, the Directors shall be empowered during each prescribed period to allot equity securities (as defined by the Act) wholly for cash:

(a) in connection with a rights issue; and

(b) otherwise than in connection with a rights issue up to an aggregate nominal amount equal to the Section 561 Amount (as defined below).

8.5 During each prescribed period the Company and its Directors by such authority and power may make offers or agreements which would or might require equity securities or other securities to be allotted after the expiry of such period.

8.6 For the purposes of this Article 8:

(a) **rights issue** means an offer of equity securities (as defined by the Act) open for acceptance for a period fixed by the Board to holders of equity securities on the Register on a fixed record date in proportion to their respective holdings of such securities or in accordance with the rights attached to them but subject to such exclusions or other arrangements as the Board may deem necessary or expedient with regard to treasury shares, fractional entitlements or legal or practical problems under the laws of any territory or under the requirements of any recognised regulatory body or stock exchange in any territory;

(b) **prescribed period** means any period (not exceeding five years on any occasion) for which the authority, in the case of Article 8.3, is conferred or renewed by ordinary or special resolution stating the Section 551 Amount and in the case of Article 8.4 is conferred or renewed by special resolution stating the Section 561 Amount;

(c) **Section 551 Amount** means for any prescribed period, the amount stated in the relevant ordinary or special resolution;

(d) **Section 561 Amount** means for any prescribed period, the amount stated in the relevant special resolution; and

(e) the nominal amount of any securities shall be taken to be, in the case of rights to subscribe for or to convert any securities into shares of the Company, the nominal amount of such shares which may be allotted pursuant to such rights.

9 **Redeemable Shares**

Subject to the Companies Acts and to any rights attaching to existing shares, any share may be issued which can be redeemed or is liable to be redeemed at the option of the Company or the holder. The Board may determine the terms, conditions and manner of redemption of any redeemable shares which are issued. Such terms and conditions shall apply to the relevant shares as if the same were set out in these Articles.

10 **Shareholder Rights**

10.1 The Ordinary Shares shall rank pari passu as a single class. The Deferred Shares shall rank pari passu as a single class.

10.2 In the event of the liquidation, dissolution or winding up of the Company, the assets of the Company available for distribution to members shall be distributed amongst all holders of the Ordinary Shares in proportion to the number of shares held irrespective of the amount paid or credited as paid on any share.

10.3 Any:

(a) consolidation or merger of the Company with or into another entity or entities (whether or not the Company is the surviving entity) as a result of which the holders of the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board immediately prior to such sale or issue cease to own the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board;

(b) sale or transfer by the Company of all or substantially all of its assets (determined either for the Company alone or together with its subsidiaries on a consolidated basis); or

(c) sale, transfer or issuance or series of sales, transfers and/or issues of shares by the Company or the holders thereof, as a result of which the holders of the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board immediately prior to such sale or issue cease to own the Company's outstanding shares possessing the voting power (under ordinary circumstances) to elect a majority of the Board,

shall be deemed to be a liquidation, dissolution and winding up of the Company for purposes of Article 10.2 (unless the Board determine otherwise), and the holders of the Ordinary Shares shall be entitled to receive from the Company the amounts payable with respect to the Ordinary Shares on a liquidation, dissolution or winding up of the Company under Article 10.2 in cancellation of their Ordinary Shares upon the completion of any such transaction.

10.4 At a general meeting of the Company and at any separate class meeting of the holders of Ordinary Shares, where a holder of Ordinary Shares is entitled to vote, such holder is entitled to one vote for each Ordinary Share held.

10.5 A holder of Ordinary Shares is entitled to receive notice of any general meeting of the Company (and notice of any separate class meeting of the holders of Ordinary Shares) and a copy of every report, accounts, circular or other document sent out by the Company to members.

10.6 Notwithstanding any other provision of these Articles, the special rights, privileges, restrictions and limitations attaching to the Deferred Shares are as follows:

(a) the Deferred Shares shall not be entitled to any dividends or to any other right or participation in the profits of the Company;

(b) on return of assets on liquidation, the Deferred Shares shall confer on the holders thereof an entitlement to receive out of the assets of the Company available for distribution amongst the members (subject to the rights of any new class of shares with preferred rights) the amount paid up or credited as paid up on the deferred shares held by them respectively after (but only after) payment shall have been made to the holders of the Ordinary Shares of the amounts paid up or credited as paid up on such shares and the sum of £1,000,000 in respect of each Ordinary Share held by them respectively. The Deferred Shares shall confer on the holders thereof no further right to participate in the assets of the Company;

(c) the Deferred Shares do not entitle the holder thereof to vote upon any resolution or to receive notice of, attend any general meeting, or be part of the quorum thereof as the holders of the Deferred Shares;

(d) any reduction of capital involving the cancellation of the Deferred Shares for no consideration shall not be deemed to be a variation of the rights attaching to them nor a modification or abrogation of the rights or privileges attaching to the Deferred Shares;

(e) the special rights conferred upon the holders of the Deferred Shares shall be deemed not to be modified, varied or abrogated by the creation or issue of further shares ranking pari passu with or in priority to the Deferred Shares;

(f) the Deferred Shares shall not be entitled to be reissued with a share certificate;

(g) no transfer of any Deferred Shares shall be permitted save as provided in Article 10.6(h);

(h) the Company shall have irrevocable authority at any time to appoint any person to execute on behalf of the holders of the Deferred Shares a transfer thereof and/or an agreement to transfer the same, without making any payment to the holders thereof, or to such person as the Company may determine as custodian thereof and/or to cancel the same without making any payment to the holders thereof and/or acquire the same (in accordance with the provisions of the Act) without making any payment to or obtaining the sanction of the holders thereof; and

(i) subject to the Act, the Company shall be entitled to purchase any Deferred Shares in issue at any time for no consideration.

11 **Pari Passu Issues**

If new shares are created or issued which rank equally with any other existing shares, the rights of the existing shares will not be regarded as changed or abrogated unless the terms of the existing shares expressly say otherwise.

12 **Variation of Rights**

12.1 Subject to the Companies Acts, the rights attached to any class of shares can be varied or abrogated either with the consent in writing of the holders of not less than three-quarters in nominal value of the issued share of that class (excluding any shares of that class held as treasury shares) or with the authority of a special resolution passed at a separate meeting of the holders of the relevant class of shares known as a **class meeting**.

12.2 The provisions of this Article will apply to any variation or abrogation of rights of shares forming part of a class. Each part of the class which is being treated differently is treated as a separate class in applying this Article.

12.3 All the provisions in these Articles as to general meetings shall apply, with any necessary modifications, to every class meeting except that:

(a) the quorum at every such meeting shall not be less than two persons holding or representing by proxy at least one-third of the nominal amount paid up on the issued shares of the class) (excluding any shares of that class held as treasury shares); and

(b) if at any adjourned meeting of such holders such quorum as set out above is not present, at least one person holding shares of the class who is present in person or by proxy shall be a quorum.

12.4 The Board may convene a class meeting whenever it thinks fit and whether or not the business to be transacted involves a variation or abrogation of class rights.

13 **Payment of Commission**

The Company may in connection with the issue of any shares or the sale for cash of treasury shares exercise all powers of paying commission and brokerage conferred or permitted by the Companies Acts. Any such commission or brokerage may be satisfied by the payment of cash or by the allotment of fully or partly paid shares or other securities or the grant of an option to call for an allotment of shares or any combination of such methods.

14 **Trusts Not Recognised**

Except as otherwise expressly provided by these Articles, required by law or as ordered by a court of competent jurisdiction, the Company shall not recognise any person as holding any share on any trust, and the Company shall not be bound by or required in any way to recognise (even when having notice of it) any equitable, contingent, future, partial or other claim to or interest in any share other than an absolute right of the holder of the whole of the share.

15 **Uncertificated Shares**

15.1 Under and subject to the uncertificated securities rules, the Board may permit title to shares of any class to be evidenced otherwise than by certificate and title to shares of such a class to be transferred by means of a relevant system and may make arrangements for a class of shares (if all shares of that class are in all respects identical) to become a participating class. Title to shares of a particular class may only be evidenced otherwise than by a certificate where that class of shares is at the relevant time a participating class. The Board may also, subject to compliance with the uncertificated securities rules, determine at any time that title to any class of shares may from a date specified by the Board no longer be evidenced otherwise than by a certificate or that title to such a class shall cease to be transferred by means of any particular relevant system.

15.2 In relation to a class of shares which is a participating class and for so long as it remains a participating class, no provision of these Articles shall apply or have effect to the extent that it is inconsistent in any respect with:

(a) the holding of shares of that class in uncertificated form;

(b) the transfer of title to shares of that class by means of a relevant system; or

(c) any provision of the uncertificated securities rules,

and, without prejudice to the generality of this Article, no provision of these Articles shall apply or have effect to the extent that it is in any respect inconsistent with the maintenance, keeping or entering up by the Operator, so long as that is permitted or required by the uncertificated securities rules, of an Operator register of securities in respect of that class of shares in uncertificated form.

15.3 Ordinary Shares of a class which is at the relevant time a participating class may be changed from uncertificated to certificated form, and from certificated to uncertificated form, in accordance with and subject as provided in the uncertificated securities rules.

15.4 If, under these Articles or the Companies Acts, the Company is entitled to sell, transfer or otherwise dispose of, forfeit, re-allot, accept the surrender of or otherwise enforce a lien over an uncertificated share, then, subject to these Articles and the Companies Acts, such entitlement shall include the right of the Board to:

(a) require the holder of the uncertificated share by notice in writing to change that share from uncertificated to certificated form within such period as may be specified in the notice and keep it as a certificated share for as long as the Board requires;

(b) appoint any person to take such other steps, by instruction given by means of a relevant system or otherwise, in the name of the holder of such share as may be required to effect the transfer of such share and such steps shall be as effective as if they had been taken by the registered holder of that share; and

(c) take such other action that the Board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of that share or otherwise to enforce a lien in respect of that share.

15.5 Unless the Board determines otherwise, shares which a member holds in uncertificated form shall be treated as separate holdings from any shares which that member holds in certificated form but a class of shares shall not be treated as two classes simply because some shares of that class are held in certificated form and others in uncertificated form.

15.6 Unless the Board determines otherwise or the uncertificated securities rules require otherwise, any shares issued or created out of or in respect of any uncertificated shares shall be uncertificated shares and any shares issued or created out of or in respect of any certificated shares shall be certificated shares.

15.7 The Company shall be entitled to assume that the entries on any record of securities maintained by it in accordance with the uncertificated securities rules and regularly reconciled with the relevant Operator register of securities are a complete and accurate reproduction of the particulars entered in the Operator register of securities and shall accordingly not be liable in respect of any act or thing done or omitted to be done by or on behalf of the Company in reliance on such assumption. Any provision of these Articles which requires or envisages that action will be taken in reliance on information contained in the Register shall be construed to permit that action to be taken in reliance on information contained in any relevant record of securities (as so maintained and reconciled).

16 **Share Certificates**

16.1 Every person (except a person to whom the Company is not by law required to issue a certificate) whose name is entered in the Register as a holder of any certificated shares shall be entitled, without charge, to receive within the time limits prescribed by the Companies Acts (unless the terms of issue prescribe otherwise) one certificate for all of the shares of that class registered in his name.

16.2 The Company shall not be bound to issue more than one certificate in respect of shares held jointly by two or more persons. Delivery of a certificate to the person first named in the Register shall be sufficient delivery to all joint holders.

16.3 Where a member has transferred part only of the shares comprised in a certificate, he shall be entitled without charge to a certificate for the balance of such shares to the extent that the balance is to be held in certificated form. Where a member receives more shares of any class, he shall be entitled without charge to a certificate for the extra shares of that class to the extent that the balance is to be held in certificated form.

16.4 A share certificate may be issued under Seal (by affixing the Seal to or printing the Seal or a representation of it on the certificate) or signed by at least two Directors or by at least one Director and the Secretary. Such certificate shall specify the number and class of the shares in respect of which it is issued and the amount or respective amounts paid up on it. The Board may be resolution decide, either generally or in any particular case or cases, that any signatures on any share certificates need not be autographic but may be applied to the certificates by some mechanical or other means or may be printed on them or that the certificates need not be signed by any **person**.

16.5 Every share certificate sent in accordance with these Articles will be sent at the risk of the member or other person entitled to the certificate. The Company will not be responsible for any share certificate lost or delayed in the course of delivery.

16.6 No share certificates shall be issued in respect of the Deferred Shares.

17 **Replacement Certificates**

17.1 Any two or more certificates representing shares of any one class held by any member may at his request be cancelled and a single new certificate for such shares issued in lieu without charge on surrender of the original certificates for cancellation.

17.2 Any certificate representing shares of any one class held by any member may at his request be cancelled and two or more certificates for such shares may be issued instead.

17.3 If a share certificate is defaced, worn out or said to be stolen, lost or destroyed, it may be replaced on such terms as to evidence and indemnity as the Board may decide and, where it is defaced or worn out, after delivery of the old certificate to the Company.

17.4 The Board may require the payment of any exceptional out-of-pocket expenses of the Company incurred in connection with the issue of any certificates under this Article. In the case of shares held jointly by several persons, any such request as is mentioned in this Article may be made by any one of the joint holders.

18 **Lien on Shares not Fully Paid**

The Company shall have a first and paramount lien on every share, not being a fully paid share, for all amounts payable to the Company (whether presently or not) in respect of that share. The Company's lien over a share takes priority over any third party's interest in that share, and extends to any dividend or other money payable by the Company in respect of that share (and, if the lien is enforced and the share is sold by the Company, the proceeds of sale of that share). The Board may at any time, either generally or in any particular case, waive any lien that has arisen or declare any share to be wholly or in part exempt from the provisions of this Article.

19 **Enforcement of Lien by Sale**

The Company may sell, in such manner as the Board may decide, any share over which the Company has a lien if a sum in respect of which the lien exists is presently payable and is not paid within 14 clear days after a notice has been served on the holder of the share or the person who is entitled by transmission to the share, demanding payment and stating that if the notice is not complied with the share may be sold. For giving effect to the sale, in the case of a certificated share, the Board may authorise some person to sign an instrument of transfer of the share sold to, or in accordance with the directions, of the buyer. In the case of an uncertificated share, the Board may require the Operator to convert the share into certificated form and after such conversion, authorise any person to sign the instrument of transfer of the share to affect the sale of the share. The buyer shall not be bound to see to the application of the purchase money, nor shall his title to the share be affected by any irregularity or invalidity in the proceedings in reference to the sale.

20 **Application of Proceeds of Sale**

The net proceeds of any sale of shares subject to any lien, after payment of the costs, shall be applied:

(a) first, in or towards satisfaction of so much of the amount due to the Company or of the liability or engagement (as the case may be) as is presently payable or is liable to be presently fulfilled or discharged; and

(b) second, any residue shall be paid to the person who was entitled to the share at the time of the sale but only after the certificate for the shares sold has been surrendered to the company for cancellation, or an indemnity in a form reasonably satisfactory to the directors has been given for any lost certificates, and subject to a like lien for debts or liabilities not presently payable as existed on the share prior to the sale.

21 **Calls**

21.1 Subject to these Articles and the terms on which the shares are allotted, the Board may from time to time make calls on the members in respect of any monies unpaid on their shares (whether in respect of nominal value or premium) and not payable on a date fixed by or in accordance with the terms of issue.

21.2 Each member shall (subject to the Company serving upon him at least 14 clear days' notice specifying when and where payment is to be made and whether or not by instalments) pay to the Company as required by the notice the amount called on for his shares.

21.3 A call shall be deemed to have been made at the time when the resolution of the Board authorising the call was passed.

21.4 A call may be revoked or postponed, in whole or in part, as the Board may decide.

21.5 Liability to pay a call is not extinguished or transferred by transferring the shares in respect of which the call is required to be paid.

22 **Liability of Joint Holders**

The joint holders of a share shall be jointly and severally liable to pay all calls in respect of the share.

23 **Interest on Calls**

If a call remains unpaid after it has become due and payable, the person from whom it is due and payable shall pay all expenses that have been incurred by the Company by reason of such non-payment together with interest on the amount unpaid from the day it is due and payable to the time of actual payment at such rate (not exceeding the Bank of England base rate by more than five percentage points) as the Board may decide. The Board may waive payment of the interest or the expenses in whole or in part.

24 **Power to Differentiate**

On or before the issue of shares, the Board may decide that allottees or holders of shares can be called on to pay different amounts or that they can be called on at different times.

25 **Payment of Calls in Advance**

The Board may, if it thinks fit, receive from any member willing to advance the same, all or any part of the monies uncalled and unpaid on the shares held by him. Such payment in advance of calls shall, to the extent of the payment, extinguish the liability on the shares on which it is made. The Company may pay interest on the money paid in advance, or so much of it as exceeds the amount for the time being called upon the shares in respect of which such advance has been made, at such rate as the Board may decide. The Board may at any time repay the amount so advanced by giving at least three months' notice in writing to such member of its intention to do so, unless before the expiration of such notice the amount so advanced shall have been called up on the shares in respect of which it was advanced.

26 **Notice if Call or Instalment Not Paid**

If any member fails to pay the whole of any call (or any instalment of any call) by the date when payment is due, the Board may at any time give notice in writing to such member (or to any person entitled to the shares by transmission), requiring payment of the amount unpaid (and any accrued interest and any expenses incurred by the Company by reason of such non-payment) by a date not less than 14 clear days from the date of the notice. The notice shall name the place where the payment is to be made and state that, if the notice is not complied with, the shares in respect of which such call was made will be liable to be forfeited.

27 **Forfeiture for Non-Compliance**

If the notice referred to in Article 26 is not complied with, any share for which it was given may be forfeited, by resolution of the Board to that effect, at any time before the payment required by the notice has been made. Such forfeiture shall include all dividends declared or other monies payable in respect of the forfeited shares and not paid before the forfeiture.

28 **Notice After Forfeiture**

When any share has been forfeited, notice of the forfeiture shall be served on the holder of the share or the person entitled to such share by transmission (as the case may be) before forfeiture. An entry of such notice having been given and of the forfeiture and the date of forfeiture shall immediately be made in the Register in respect of such share. However, no forfeiture shall be invalidated by any omission to give such notice or to make such entry in the Register.

29 **Forfeiture May Be Annulled**

The Board may annul the forfeiture of a share, at any time before any forfeited share has been cancelled or sold, re-allotted or otherwise disposed of, on the terms that payment shall be made of all calls and interest due on it and all expenses incurred in respect of the share and on such further terms (if any) as the Board shall see fit.

30 **Surrender**

The Board may accept the surrender of any share liable to be forfeited and, in any event, references in these Articles to forfeiture shall include surrender.

31 **Sale of Forfeited Shares**

31.1 A forfeited share shall become the property of the Company.

31.2 Subject to the Companies Acts, any such share may be sold, re-allotted or otherwise disposed of, on such terms and in such manner as the Board thinks fit.

31.3 The Board may, for the purposes of the disposal, authorise some person to transfer the share in question and may enter the name of the transferee in respect of the transferred share in the Register even if no share certificate is lodged and may issue a new certificate to the transferee. An instrument of transfer executed by that person shall be as effective as if it had been executed by the holder of or the person entitled by transmission to, the share. The Company may receive the consideration (if any) given for the share on its disposal.

32 **Effect of Forfeiture**

A member whose shares have been forfeited shall cease to be a member in respect of such forfeited shares and shall surrender the certificate for such shares to the Company for cancellation. Such member shall remain liable to pay to the Company all sums which at the date of forfeiture were presently payable by him to the Company in respect of such shares with interest (not exceeding the Bank of England base rate by two percentage points) from the date of the forfeiture to the date of payment. The Directors may waive payment of interest wholly or in part and may enforce payment, without any reduction or allowance for the value of the shares at the time of forfeiture or for any consideration received on their disposal.

33 **Evidence of Forfeiture**

A statutory declaration by a Director or the Secretary that a share has been forfeited on a specified date shall be conclusive evidence of the facts stated in it as against all persons claiming to be entitled to the share. The declaration shall (subject to the execution of an instrument of transfer if necessary) constitute a good title to the share. The person to whom the share is transferred or sold shall not be bound to see to the application of the purchase money or other consideration (if any), nor shall his title to the share be affected by any act, omission or irregularity relating to or connected with the proceedings in reference to the forfeiture or disposal of the share.

34 **Form of Transfer**

34.1 Subject to these Articles:

(a) each member may transfer all or any of his shares which are in certificated form by instrument of transfer in writing in any usual form or in any form approved by the Board. Such instrument shall be executed by or on behalf of the transferor and (in the case of a transfer of a share which is not fully paid up) by or on behalf of the transferee. All instruments of transfer, when registered, may be retained by the Company.

(b) each member may transfer all or any of his shares which are in uncertificated form by means of a relevant system in such manner provided for, and subject as provided in, the uncertificated securities rules. No provision of these Articles shall apply in respect of an uncertificated share to the extent that it requires or contemplates the effecting of a transfer by an instrument in writing or the production of a certificate for the share to be transferred.

34.2 The transferor of a share shall be deemed to remain the holder of the share concerned until the name of the transferee is entered in the Register in respect of it.

35 **Right to Refuse Registration of Transfer**

35.1 The Board may, in its absolute discretion, refuse to register any transfer of a share in certificated form (or renunciation of a renounceable letter of allotment) unless:

(a) it is for a share which is fully paid up;

(b) it is for a share upon which the Company has no lien;

(c) it is only for one class of share;

(d) it is in favour of a single transferee or no more than four joint transferees;

(e) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the Board to be exempt from stamp duty (if this is required); and

(f) is delivered for registration to the Office (or such other place as the Board may determine), accompanied (except in the case of a transfer by a person to whom the Company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the Board may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

35.2 The Board shall not refuse to register any transfer or renunciation of partly paid shares which are admitted to, or for which certificated or uncertificated depositary instruments over such shares are admitted to, NASDAQ on the grounds that they are partly paid shares in circumstances where such refusal would prevent dealings in such shares from taking place on an open and proper basis.

35.3 Transfers of shares will not be registered in the circumstances referred to in Article 72.

35.4 The Board may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the uncertificated securities rules and the relevant system.

36 **Notice of Refusal to Register a Transfer**

If the Board refuses to register a transfer of a share it shall notify the transferee of the refusal and the reasons for it within two months after the date on which the transfer was lodged with the Company or the instructions to the relevant system received. Any instrument of transfer which the Board refuses to register shall be returned to the person depositing it (except if there is suspected or actual fraud). All instruments of transfer which are registered may be retained by the Company.

37 **No Fees on Registration**

No fee shall be charged for registration of a transfer or other document or instruction relating to or affecting the title to any share or for making any other entry in the Register.

38 **Other Powers in Relation to Transfers**

Nothing in these Articles shall prevent the Board:

(a) from recognising a renunciation of the allotment of any share by the allottee in favour of another person; or

(b) (if empowered to do so by these Articles) from authorising any person to execute an instrument of transfer of a share and from authorising any person to transfer that share in accordance with any procedures implemented under Article 19.

39 **Transmission of Shares on Death**

If a member dies, the survivors or survivor (where he was a joint holder), and his executors or administrators (where he was a sole or the only survivor of joint holders), shall be the only persons recognised by the Company as having any title to his shares. Nothing in these Articles shall release the estate of a deceased member from any liability for any share which has been solely or jointly held by him.

40 **Election of Person Entitled By Transmission**

40.1 Any person becoming entitled to a share because of the death or bankruptcy of a member, or otherwise by operation of law, may (on such evidence as to his title being produced as the Board may require) elect either to become registered as a member or to have some person nominated by him registered as a member. If he elects to become registered himself, he shall notify the Company to that effect. If he elects to have some other person registered, he shall execute an instrument of transfer of such share to that person. All the provisions of these Articles relating to the transfer of shares shall apply to the notice or instrument of transfer (as the case may be) as if it were an instrument of transfer executed by the member and his death, bankruptcy or other event had not occurred. Where the entitlement of a person to a share because of the death or bankruptcy of a member or otherwise by operation of law is proved to the satisfaction of the Board, the Board shall within 30 days after proof cause the entitlement of that person to be noted in the Register.

40.2 A person entitled by transmission to a share in uncertificated form who elects to have some other person registered shall either:

(a) procure that instructions are given by means of the relevant system to effect transfer of such uncertificated share to that person; or

(b) change the uncertificated share to certificated form and execute an instrument of transfer of that certificated share to that person.

41 **Rights on Transmission**

Where a person becomes entitled to a share because of the death or bankruptcy of any member, or otherwise by operation of law, the rights of the holder in relation to such share shall cease. However, the person so entitled may give a good discharge for any dividends and other monies payable in respect of it and shall have the same rights to which he would be entitled if he were the holder of the share, except that he shall not be entitled to receive notice of, or to attend or vote at, any meeting of the Company or any separate meeting of the holders of any class of shares of the Company before he is registered as the holder of the share. The Board may at any time give notice requiring any such person to elect either to be registered himself or to transfer the share. If the notice is not complied with within 30 days, the Board may withhold payment of all dividends and the other monies payable in respect of such share until the requirements of the notice have been complied with.

42 **Destruction of Documents**

42.1 The Company may destroy any:

(a) instrument of transfer, after six years from the date on which it is registered;

(b) dividend mandate or any variation or cancellation of a dividend mandate or any notification of change of name or address, after two years from the date on which it is recorded;

(c) share certificate, after one year from the date on which it is cancelled;

(d) instrument of proxy which has been used for the purpose of a poll at any time after one year has elapsed from the date of use;

(e) instrument of proxy which has not been used for the purpose of a poll at any time after a period of one month has elapsed from the end of the meeting to which the instrument of proxy relates;

(f) Share Warrant (including coupons or tokens detailed from it) which has been cancelled at any time after seven years from the date on which it was cancelled; or

(g) other document for which any entry in the Register is made, after six years from the date on which an entry was first made in the Register in respect of it,

provided that the Company may destroy any such type of document at a date earlier than that authorised by this Article if a copy of such document is made and retained (whether electronically, by microfilm, by digital imaging or by other similar means) until the expiration of the period applicable to the destruction of the original of such document.

42.2 It shall be conclusively presumed in favour of the Company that every:

(a) entry in the Register purporting to have been made on the basis of a document so destroyed was duly and properly made;

(b) instrument of transfer so destroyed was duly registered;

(c) share certificate so destroyed was duly cancelled; and

(d) other document so destroyed had been properly dealt with under its terms and was valid and effective according to the particulars in the records of the Company.

42.3 This Article shall only apply to the destruction of a document in good faith and without notice of any claim (regardless of the parties to it) to which the document might be relevant. Nothing in this Article shall be construed as imposing any liability on the Company in respect of the destruction of any such document other than as provided for in this Article which would not attach to the Company in the absence of this Article. References in this Article to the destruction of any document include references to the disposal of it in any manner.

42.4 References in this Article to instruments of transfer shall include, in relation to uncertificated shares, instructions and/or notifications made in accordance with the relevant system relating to the transfer of such shares.

43 **Sub-Division**

Any resolution authorising the Company to sub-divide its shares or any of them may determine that, as between the shares resulting from the sub-division, any of them may have any preference or advantage or be subject to any restriction as compared with the others.

44 **Fractions**

If any shares are consolidated or consolidated and then divided, the Board has power to deal with any fractions of shares which result. If the Board decides to sell any shares representing fractions, it can do so for the best price reasonably obtainable and distribute the net proceeds of sale among members in proportion to their fractional entitlements. The Board can arrange for any shares representing fractions to be entered in the Register as certificated shares if they consider that this makes it easier to sell them. The Board can sell those shares to anyone, including the Company if the legislation allows, and may authorise any person to transfer or deliver the shares to the buyer or in accordance with the buyer's instructions. The buyer shall not be bound to see to the application of the purchase money, nor shall his title to the share be affected by any irregularity or invalidity in the proceedings in reference to the sale.

45 **Annual General Meetings**

An annual general meeting shall be held once a year, at such time (consistent with the terms of the Companies Acts) and place as may be determined by the Board.

46 **Convening of General Meetings**

All meetings other than annual general meetings shall be called general meetings. The Board may, whenever it thinks fit, and shall on requisition in accordance with the Companies Acts, proceed to convene a general meeting.

47 **Notice of General Meetings**

A general meeting shall be called by at least such minimum notice as is required or permitted by the Companies Acts. The period of notice shall in either case be exclusive of the day on which it is served or deemed to be served and of the day on which the meeting is to be held and shall be given to all members other than those who are not entitled to receive such notices from the Company. The Company may give such notice by any means or combination of means permitted by the Companies Acts.

48 **Contents of Notice of Meetings**

48.1 Every notice calling a meeting shall specify the place, date and time of the meeting, and there shall appear with reasonable prominence in every such notice a statement that a member entitled to attend and vote is entitled to a proxy or (if he has more than one share) proxies to exercise all or any of his rights to attend, speak and vote and that a proxy need not be a member of the Company. Such notice shall also include the address of the website on which the information required by the Act is published, state the procedures with which members must comply in order to be able to attend and vote at the meeting (including the date by which they must comply), provide details of any forms to be used for the appointment of a proxy and state that a member has the right to ask questions at the meeting in accordance with the Act.

48.2 The notice shall specify the general nature of the business to be transacted at the meeting and shall set out the text of all resolutions to be considered by the meeting and shall state in each case whether it is proposed as an ordinary resolution or as a special resolution.

48.3 In the case of an annual general meeting, the notice shall also specify the meeting as such.

48.4 For the purposes of determining which persons are entitled to attend or vote at a meeting and how many votes a person may cast, the Company may specify in the notice of meeting a time, not more than 48 hours before the time fixed for the meeting (not taking into account non-working days) by which a person must be entered in the Register in order to have the right to attend or vote at the meeting or appoint a proxy to do so.

49 **Omission to Give Notice and Non-Receipt of Notice**

The accidental omission to give notice of any meeting or to send an instrument of proxy (where this is intended to be sent out with the notice) to or the non-receipt of either by, any person entitled to receive the same shall not invalidate the proceedings of that meeting.

50 **Postponement of General Meeting**

If the Board considers that it is impracticable or unreasonable to hold a general meeting on the date or at the time or place stated in the notice calling the meeting, it may postpone or move the meeting (or do both). The Board shall take reasonable steps to ensure that notice of the date, time and place of the rearranged meeting is given to any member trying to attend the meeting at the original time and place. Notice of the date, time and place of the rearranged meeting shall, if practicable, also be placed in at least two national newspapers published in the United Kingdom. Notice of the business to be transacted at such rearranged meeting shall not be required. If a meeting is rearranged in this way, appointments of proxy are valid if they are received as required by these Articles not less than 48 hours before the time appointed for holding the rearranged meeting and for the purpose of calculating this period, the Board can decide in their absolute discretion, not to take account of any part of a day that is not a working day. The Board may also postpone or move the rearranged meeting (or do both) under this Article.

51 **Quorum at General Meeting**

No business shall be transacted at any general meeting unless a quorum is present. If a quorum is not present a chairman of the meeting can still be chosen and this will not be treated as part of the business of the meeting. Two members present in person or by proxy and entitled to attend and to vote on the business to be transacted shall be a quorum.

52 **Procedure if Quorum Not Present**

If a quorum is not present within 15 minutes (or such longer interval as the chairman in his absolute discretion thinks fit) from the time appointed for holding a general meeting, or if a quorum ceases to be present during a meeting, the meeting shall be dissolved if convened on the requisition of members. In any other case, the meeting shall stand adjourned to another day, (not being less than ten clear days after the date of the original meeting), and at such time and place as the chairman (or, in default, the Board) may determine. If at such adjourned meeting a quorum is not present within 15 minutes from the time appointed for holding the meeting, one person entitled to vote on the business to be transacted, being a member or a proxy for a member or a duly authorised representative of a corporation which is a member, shall be a quorum and any notice of an adjourned meeting shall state this.

53 **Chairman of General Meeting**

53.1 The chairman of the Board shall preside at every general meeting of the Company. If there is no such chairman or if at any meeting he shall not be present within five minutes after the time appointed for holding the meeting, or shall be unwilling to act as chairman, the deputy chairman (if any) of the Board shall, if present and willing to act, preside at such meeting. If more than one deputy chairman is present they shall agree amongst themselves who is to take the chair or, if they cannot agree, the deputy chairman who has been in office as a director the longest shall take the chair.

53.2 If no chairman or deputy chairman shall be so present and willing to act, the Directors present shall choose one of their number to act or, if there be only one Director present, he shall be chairman if willing to act. If there be no Director present and willing to act, the members present and entitled to vote shall choose one of their number to be chairman of the meeting. Nothing in these Articles shall restrict or exclude any of the powers or rights of a chairman of a meeting which are given by law.

54 **Entitlement to Attend and Speak**

A Director (and any other person invited by the chairman to do so) may attend and speak at any general meeting and at any separate meeting of the holders of any class of shares of the Company, whether or not he is a member.

55 **Adjournments**

The chairman may, with the consent of a meeting at which a quorum is present, and shall, if so directed by the meeting, adjourn any meeting from time to time (or indefinitely) and from place to place as the meeting shall determine. However, without prejudice to any other power which he may have under these Articles or at common law, the chairman may, without the need for the consent of the meeting, interrupt or adjourn any meeting from time to time and from place to place or for an indefinite period if he is of the opinion that it has become necessary to do so in order to secure the proper and orderly conduct of the meeting or to give all persons entitled to do so a reasonable opportunity of attending, speaking and voting at the meeting or to ensure that the business of the meeting is properly disposed of.

56 **Notice of Adjournment**

If the meeting is adjourned indefinitely or for more than three months, notice of the adjourned meeting shall be given in the same manner as in the case of the original meeting. Except as provided in these Articles, there is no need to give notice of the adjourned meeting or of the business to be considered there.

57 **Business of Adjourned Meeting**

No business shall be transacted at any adjourned meeting other than the business which might properly have been transacted at the meeting from which the adjournment took place.

58 **Security Arrangement and Orderly Conduct**

58.1 The Board may direct that any person wishing to attend any meeting should provide such evidence of identity and submit to such searches or other security arrangements or restrictions as the Board shall consider appropriate in the circumstances and shall be entitled in its absolute discretion to refuse entry to any meeting to any person who fails to provide such evidence of identity or to submit to such searches or to otherwise comply with such security arrangements or restrictions.

58.2 The chairman shall take such action or give directions as he thinks fit to promote the orderly conduct of the business of the meeting as laid down in the notice of the meeting and to ensure the security of the meeting and the safety of the people attending the meeting. The chairman's decision on matters of procedure or arising incidentally from the business of the meeting shall be final as shall be his determination as to whether any matter is of such a nature.

59 **Overflow Meeting Rooms**

59.1 The Board may, in accordance with this Article, make arrangements for members and proxies who are entitled to attend and participate in a general meeting, but who cannot be seated in the main meeting room where the chairman will be, to attend and take part in a general meeting in an overflow room or rooms. Any overflow room will have appropriate links to the main room and will enable audio-visual communication between the meeting rooms throughout the meeting. The Board will decide how to divide members and proxies between the main room and the overflow room. If an overflow room is used, the meeting will be treated as being held and taking place in the main meeting room and the meeting will consist of all the members and proxies who are attending both in the main meeting room and the overflow room.

59.2 Details of any arrangements for overflow rooms will be set out in the notice of the meeting but failure to do so will not invalidate the meeting.

60 **Satellite Meeting Places**

60.1 To facilitate the organisation and administration of any general meeting, the Board may decide that the meeting shall be held at two or more locations.

60.2 For the purposes of these Articles, any general meeting of the Company taking place at two or more locations shall be treated as taking place where the chairman of the meeting presides (the **principal meeting place**) and any other location where that meeting takes place is referred in these Articles as a **satellite meeting**.

60.3 A member present in person or by proxy at a satellite meeting may be counted in the quorum and may exercise all rights that they would have been able to exercise if they were present at the principal meeting place.

60.4 The Board may make and change from time to time such arrangements as they shall in their absolute discretion consider appropriate to:

(a) ensure that all members and proxies for members wishing to attend the meeting can do so;

(b) ensure that all persons attending the meeting are able to participate in the business of the meeting and to see and hear anyone else addressing the meeting;

(c) ensure the safety of persons attending the meeting and the orderly conduct of the meeting; and

(d) restrict the numbers of members and proxies at any one location to such number as can safely and conveniently be accommodated there.

60.5 The entitlement of any member or proxy to attend a satellite meeting shall be subject to any such arrangements then in force and stated by the notice of the meeting or adjourned meeting to apply to the meeting.

60.6 If there is a failure of communication equipment or any other failure in the arrangements for participation in the meeting at more than one place, the chairman may adjourn the meeting in accordance with Article 55. Such adjournment will not affect the validity of such meeting, or any business conducted at such meeting up to the point of adjournment, or any action taken pursuant to such meeting.

60.7 A person (**satellite chairman**) appointed by the Board shall preside at each satellite meeting. Every satellite chairman shall carry out all requests made of him by the chairman of the meeting, may take such action as he thinks necessary to maintain the proper and orderly conduct of the satellite meeting and shall have all powers necessary or desirable for such purposes.

61 **Amendment to Resolutions**

61.1 If an amendment to any resolution under consideration is proposed but is ruled out of order by the chairman of the meeting in good faith, any error in such ruling shall not invalidate the proceedings on the original resolution.

61.2 In the case of a resolution duly proposed as a special resolution, no amendment to it (other than an amendment to correct a patent error) may in any event be considered or voted on. In the case of a resolution duly proposed as an ordinary resolution no amendment to it (other than an amendment to correct a patent error) may be considered or voted on unless either at least 48 hours prior to the time appointed for holding the meeting or adjourned meeting at which such ordinary resolution is to be proposed, notice in writing of the terms of the amendment and intention to move the same has been lodged at the Office or received in electronic form at the electronic address at which the Company has or is deemed to have agreed to receive it or the chairman of the meeting in his absolute discretion decides that it may be considered or voted on.

62 **Members' Resolutions**

62.1 Members of the Company shall have the rights provided by the Companies Acts to have the Company circulate and give notice of a resolution which may be properly moved, and is intended to be moved, at the Company's next annual general meeting.

62.2 Expenses of complying with these rights shall be borne in accordance with the Companies Acts.

63 **Method of Voting**

63.1 At any general meeting a resolution put to a vote of the meeting shall be decided on a show of hands, unless (before or on the declaration of the result of the show of hands) a poll is duly demanded. Subject to the Companies Acts, a poll may be demanded by:

(a) the chairman of the meeting; or

(b) at least two members present in person (or by proxy) and entitled to vote at the meeting; or

(c) a member or members present in person (or by proxy) representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting; or

(d) a member or members present in person (or by proxy) holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

63.2 The chairman of the meeting may also demand a poll before a resolution is put to the vote on a show of hands.

63.3 At general meetings, resolutions shall be put to the vote by the chairman of the meeting and there shall be no requirement for the resolution to be proposed or seconded by any person.

63.4 Unless a poll is duly demanded and the demand is not withdrawn, a declaration by the chairman of the meeting that a resolution has on a show of hands been carried, or carried unanimously or by a particular majority, or lost, or not carried by a particular majority, and an entry to that effect in the book containing the minutes of proceedings of the Company, shall be conclusive evidence of the fact, without proof of the number or proportion of the votes recorded in favour of or against such resolution.

64 **Objection to Error in Voting**

No objection shall be raised to the qualification of any voter or to the counting of, or failure to count, any vote, except at the meeting or adjourned meeting at which the vote objected to is given or tendered or at which the error occurs. Any objection or error shall be referred to the chairman of the meeting and shall only vitiate the decision of the meeting on any resolution if the chairman decides that the same is of sufficient magnitude to vitiate the resolution or may otherwise have affected the decision of the meeting. The decision of the chairman of the meeting on such matters shall be final and conclusive.

65 **Procedure on a Poll**

65.1 Any poll duly demanded on the election of a chairman or on any question of adjournment shall be taken immediately. A poll duly demanded on any other matter shall be taken in such manner (including the use of ballot or voting papers or tickets) and at such time and place, not more than 30 days from the date of the meeting or adjourned meeting at which the poll was demanded, as the chairman shall direct. The chairman may appoint scrutineers who need not be members. It is not necessary to give notice of a poll not taken immediately if the time and place at which it is to be taken are announced at the meeting at which it is demanded. In any other case, at least seven clear days' notice shall be given specifying the time, date and place at which the poll shall be taken. The result of the poll shall be deemed to be the resolution of the meeting at which the poll was demanded.

65.2 The demand for a poll (other than on the election of a chairman or any question of adjournment) shall not prevent the continuance of the meeting for the transaction of any business other than the question on which a poll has been demanded.

65.3 The demand for a poll may, before the poll is taken, be withdrawn, but only with the consent of the chairman of the meeting. A demand so withdrawn validates the result of a show of hands declared before the demand was made. If a poll is demanded before the declaration of the result of a show of hands and the demand is duly withdrawn, the meeting shall continue as if the demand had not been made.

65.4 On a poll votes may be given in person or by proxy. A member entitled to more than one vote need not, if he votes, use all his votes or cast all the votes he uses in the same way.

66 **Votes of Members**

66.1 Subject to Article 66.2, the Companies Acts, to any special terms as to voting on which any shares may have been issued or may for the time being be held and to any suspension or abrogation of voting rights under these Articles, at any general meeting every member who is present in person (or by proxy) shall on a show of hands have one vote and every member present in person (or by proxy) shall on a poll have one vote for each share of which he is the holder.

66.2 On a show of hands, a duly appointed proxy has one vote for and one vote against a resolution if the proxy has been appointed by more than one member entitled to vote on the resolution and the proxy has been instructed:

(a) by one or more of those members to vote for the resolution and by one or more other of those members to vote against it; or

(b) by one or more of those members to vote either for or against the resolution and by one or more other of those members to use his/her discretion as to how to vote.

66.3 If two or more persons are joint holders of a share, then in voting on any question the vote of the senior who tenders a vote, whether in person or by proxy, shall be accepted to the exclusion of the votes of the other joint holders. For this purpose seniority shall be determined by the order in which the names of the holders stand in the Register.

66.4 Where in England or elsewhere a receiver or other person (by whatever name called) has been appointed by any court claiming jurisdiction in that behalf to exercise powers with respect to the property or affairs of any member on the ground (however formulated) of mental disorder, the Board may in its absolute discretion, upon or subject to production of such evidence of the appointment as the Board may require, permit such receiver or other person on behalf of such member to vote in person, on a show of hands or on a poll, by proxy on behalf of such member at any general meeting or to exercise any other right conferred by membership in relation to meetings of the Company. Evidence to the satisfaction of the Board of the authority of the person claiming to exercise the right to vote shall be deposited at the Office, or at such other place as is specified in accordance with these Articles for the deposit of instruments of proxy, at least 48 hours before the time appointed for holding the meeting or adjourned meeting at which the right to vote is to be exercised and, in default, the right to vote shall not be exercisable.

66.5 In the case of equality of votes whether on a show of hands or on a poll, the chairman of the meeting at which the show of hands takes place or at which the poll is demanded shall not be entitled to a casting vote.

67 **No Right to Vote Where Sums Overdue on Shares**

No member may vote at a general meeting (or any separate meeting of the holders of any class of shares), either in person or by proxy, or to exercise any other right or privilege as a member in respect of a share held by him unless:

(a) all calls or other sums presently due and payable by him in respect of that share whether alone or jointly with any other person together with interest and expenses (if any) have been paid to the Company; or

(b) the Board determines otherwise.

68 **Voting by Proxy**

68.1 Subject to Article 68.2, an instrument appointing a proxy shall be in writing in any usual form (or in another form approved by the Board) executed under the hand of the appointer or his duly constituted attorney or, if the appointer is a corporation, under its seal or signed by a duly authorised officer or attorney or other person authorised to sign.

68.2 Subject to the Companies Acts, the Board may accept the appointment of a proxy received by electronic means on such terms and subject to such conditions as it considers fit. The appointment of a proxy received by electronic means shall not be subject to the requirements of Article 68.1.

68.3 For the purposes of Articles 68.1 and 68.2, the Board may require such reasonable evidence it considers necessary to determine:

(a) the identity of the member and the proxy; and

(b) where the proxy is appointed by a person acting on behalf of the member, the authority of that person to make the appointment.

68.4 A member may appoint another person as his proxy to exercise all or any of his rights to attend and to speak and to vote (both on a show of hands and on a poll) on a resolution or amendment of a resolution, or on other business arising, at a meeting or meetings of the Company. Unless the contrary is stated in it, the appointment of a proxy shall be deemed to confer authority to exercise all such rights, as the proxy thinks fit.

68.5 A proxy need not be a member.

68.6 A member may appoint more than one proxy in relation to a meeting, provided that each proxy is appointed to exercise the rights attached to different shares held by the member. When two or more valid but differing appointments of proxy are delivered or received for the same share for use at the same meeting, the one which is last validly delivered or received (regardless of its date or the date of its execution) shall be treated as replacing and revoking the other or others as regards that share. If the Company is unable to determine which appointment was last validly delivered or received, none of them shall be treated as valid in respect of that share.

68.7 Delivery or receipt of an appointment of proxy does not prevent a member attending and voting in person at the meeting or an adjournment of the meeting or on a poll.

68.8 The appointment of a proxy shall (unless the contrary is stated in it) be valid for an adjournment of the meeting as well as for the meeting or meetings to which it relates. The appointment of a proxy shall be valid for 12 months from the date of execution or, in the case of an appointment of proxy delivered by electronic means, for 12 months from the date of delivery unless otherwise specified by the Board.

68.9 Subject to the Companies Acts, the Company may send a form of appointment of proxy to all or none of the persons entitled to receive notice of and to vote at a meeting. If sent, the form shall provide for three-way voting on all resolutions (other than procedural resolutions) set out in the notice of meeting.

69 **Receipt of Proxy**

69.1 An instrument appointing a proxy and any reasonable evidence required by the Board in accordance with Article 68.3 shall:

(a) subject to Articles 69.1(c) and (d), in the case of an instrument of proxy in hard copy form, delivered to the office, or another place in the United Kingdom specified in the notice convening the meeting or in the form of appointment of proxy or other accompanying document sent by the Company in relation to the meeting (a **proxy notification address**) not less than 48 hours before the time for holding the meeting or adjourned meeting at which the person named in the form of appointment of proxy proposes to vote;

(b) subject to Articles 69.1(c) and (d), in the case of an appointment of a proxy sent by electronic means, where the Company has given an electronic address (a proxy notification electronic address):

(i) in the notice calling the meeting;

(ii) in an instrument of proxy sent out by the Company in relation to the meeting;

(iii) in an invitation to appoint a proxy issued by the Company in relation to the meeting; or

(iv) on a website maintained by or on behalf of the Company on which any information relating to the meeting is required by the Act to be kept,

it shall be received at such proxy notification electronic address not less than 48 hours before the time for holding the meeting or adjourned meeting at which the person named in the form of appointment of proxy proposes to vote;

(c) in the case of a poll taken more than 48 hours after it is demanded, delivered or received at a proxy notification address or a proxy notification electronic address and not less than 24 hours before the time appointed for the holding of the adjourned meeting or the taking of the poll; or

(d) in the case of a poll which is not taken at the meeting at which it is demanded but is taken 48 hours or less after it is demanded, or in the case of an adjourned meeting to be held 48 hours or less after the time fixed for holding the original meeting, received:

(i) at a proxy notification address or a proxy notification electronic address in accordance with Articles 69.1(a) or (b);

(ii) by the chairman of the meeting or the secretary or any director at the meeting at which the poll is demanded or, as the case may be, at the original meeting; or

(iii) at a proxy notification address or a proxy notification electronic address by such time as the chairman of the meeting may direct at the meeting at which the poll is demanded.

In calculating the periods in this Article, no account shall be taken of any part of a day that is not a working day.

69.2 The Board may decide, either generally or in any particular case, to treat a proxy appointment as valid notwithstanding that the appointment or any of the information required under Article 68.3 has not been received in accordance with the requirements of this Article.

69.3 Subject to Article 69.2, if the proxy appointment and any of the information required under Article 68.3 is not received in the manner set out in Article 69.1, the appointee shall not be entitled to vote in respect of the shares in question.

69.4 Without limiting the foregoing, in relation to any uncertificated shares, the Board may from time to time:

(a) permit appointments of a proxy by means of a communication sent in electronic form in the form of an uncertificated proxy instruction; and

(b) permit supplements to, or amendments or revocations of, any such uncertificated proxy instruction by the same means.

The Board may in addition prescribe the method of determining the time at which any such uncertificated proxy instruction is to be treated as received by the Company or a participant acting on its behalf. The Board may treat any such uncertificated proxy instruction which purports to be or is expressed to be sent on behalf of a holder of a share as sufficient evidence of the authority of the person sending that instruction to send it on behalf of that holder.

70 **Revocation of Proxy**

A vote given or poll demanded by a proxy shall be valid in the event of the death or mental disorder of the principal or the revocation of the instrument of proxy, or of the authority under which the instrument of proxy was executed, or the transfer of the share for which the instrument of proxy is given, unless notice in writing of such death, mental disorder, revocation or transfer shall have been received by the Company at the Office, or at such other place as has been appointed for the deposit of instruments of proxy, no later than the last time at which an appointment of a proxy should have been received in order for it to be valid for use at the meeting or on the holding of the poll at which the vote was given or the poll taken.

71 **Corporate Representatives**

71.1 A corporation (whether or not a company within the meaning of the Act) which is a member may, by resolution of its directors or other governing body, authorise such person as it thinks fit to act as its representative (or, as the case may be, representatives) at any meeting of the Company or at any separate meeting of the holders of any class of shares.

71.2 Any person so authorised shall be entitled to exercise the same powers on behalf of the corporation (in respect of that part of the corporation's holdings to which the authority relates) as the corporation could exercise if it were an individual member.

71.3 The corporation shall for the purposes of these Articles be deemed to be present in person and at any such meeting if a person so authorised is present at it, and all references to attendance and voting in person shall be construed accordingly.

71.4 A Director, the Secretary or some person authorised for the purpose by the Secretary may require the representative to produce a certified copy of the resolution so authorising him or such other evidence of his authority reasonably satisfactory to them before permitting him to exercise his powers.

71.5 A vote given or a poll demanded by a corporate representative shall be valid notwithstanding that he is no longer authorised to represent the member unless notice of the revocation of appointment was delivered in writing to the Company at such place or address and by such time as is specified in Article 70 for the revocation of the appointment of a proxy.

72 **Failure to Disclose Interests in Shares**

72.1 If a member, or any other person appearing to be interested in shares held by that member, has been issued with a notice under section 793 of the Act (**section 793 notice**) and has failed in relation to any shares (**default shares,** which expression includes any shares issued after the date of such notice in right of those shares) to give the Company the information required by the section 793 notice within the prescribed period from the service of the notice, the following sanctions shall apply unless the Board determines otherwise:

(a) the member shall not be entitled in respect of the default shares to be present or to vote (either in person or by representative or proxy) at any general meeting or at any separate meeting of the holders of any class of shares or on any poll or to exercise any other right conferred by membership in relation to any such meeting or poll; and

(b) where the default shares represent at least 0.25% in nominal value of the issued shares of their class (calculated exclusive of any shares held as treasury shares):

(i) any dividend or other money payable for such shares shall be withheld by the Company, which shall not have any obligation to pay interest on it, and the member shall not be entitled to elect, pursuant to Article 130, to receive shares instead of that dividend; and

(ii) no transfer, other than an excepted transfer, of any shares held by the member shall be registered unless the member himself is not in default of supplying the required information and the member proves to the satisfaction of the Board that no person in default of supplying such information is interested in any of the shares that are the subject of the transfer.

For the purposes of ensuring Article 72.1(b)(ii) can apply to all shares held by the member, the Company may in accordance with the uncertificated securities rules, issue a written notification to the Operator requiring conversion into certificated form of any share held by the member in uncertificated form.

72.2 Where the sanctions under Article 72.1 apply in relation to any shares, they shall cease to have effect (and any dividends withheld under Article 72.1(b) shall become payable):

(a) if the shares are transferred by means of an excepted transfer but only in respect of the shares transferred; or

(b) at the end of the period of seven days (or such shorter period as the Board may determine) following receipt by the Company of the information required by the section 793 notice and the Board being fully satisfied that such information is full and complete.

72.3 Where, on the basis of information obtained from a member in respect of any share held by him, the Company issues a section 793 notice to any other person, it shall at the same time send a copy of the notice to the member, but the accidental omission to do so, or the non-receipt by the member of the copy, shall not invalidate or otherwise affect the application of Article 72.1.

72.4 For the purposes of this Article:

(a) a person, other than the member holding a share, shall be treated as appearing to be interested in that share if the member has informed the Company that the person is, or may be, so interested, or if the Company (after taking account of any information obtained from the member or, pursuant to a section 793 notice, from anyone else) knows or has reasonable cause to believe that the person is, or may be, so interested;

(b) **interested** shall be construed as it is for the purpose of section 793 of the Act;

(c) reference to a person having failed to give the Company the information required by a notice, or being in default as regards supplying such information, includes reference:

(i) to his having failed or refused to give all of any part of it; and

(ii) to his having given information which he knows to be false in a material particular or having recklessly given information which is false in a material particular;

(d) **prescribed period** means 14 days;

(e) **excepted transfer** means, in relation to any shares held by a member:

(i) a transfer by way of or pursuant to acceptance of a takeover offer for the Company (within the meaning of section 974 of the Act); or

(ii) a transfer in consequence of a sale made through a recognised investment exchange (as defined in section 285 of the FSMA) or any other stock exchange outside the United Kingdom on which the Company's shares are normally traded; or

(iii) a transfer which is shown to the satisfaction of the Board to be made in consequence of a sale of the whole of the beneficial interest in the shares to a person who is unconnected with the member and with any other person appearing to be interested in the shares.

72.5 Nothing contained in this Article shall be taken to limit the powers of the Company under section 794 of the Act.

73 **Power of Sale of Shares of Untraced Members**

73.1 The Company shall be entitled to sell at the best price reasonably obtainable any share of a member, or any share to which a person is entitled by transmission, if and provided that:

(a) during the period of 12 years before the date of sending of the notice referred to in Article 73.1(b) no cheque, order or warrant in respect of such share sent by the Company through the post in a pre-paid envelope addressed to the member or to the person entitled by transmission to the share, at his address on the Register or other last known address given by the member or person to which cheques, orders or warrants in respect of such share are to be sent has been cashed and the Company has received no communications in respect of such share from such member or person entitled, provided that during such period of 12 years the Company has paid at least three cash dividends (whether interim or final) and no such dividend has been claimed by the person entitled to it;

(b) on or after expiry of the said period of 12 years, the Company has given notice of its intention to sell such share by sending a notice to the member or person entitled by transmission to the share at his address on the Register or other last known address given by the member or person entitled by transmission to the share and before sending such a notice to the member or other person entitled by transmission, the Company must have used reasonable efforts to trace the member or other person entitled, engaging, if considered appropriate, a professional asset reunification company or other tracing agent and/or giving notice of its intention to sell the share by advertisement in a national newspaper and in a newspaper circulating in the area of the address of the member or person entitled by transmission to the share shown in the Register;

(c) during the further period of three months following the date of such notice and prior to the exercise of the power of sale the Company has not received any communication in respect of such share from the member or person entitled by transmission; and

(d) the Company has given notice to NASDAQ of its intention to make such sale, if shares of the class concerned, or certificated or uncertificated depositary instruments over such shares, are listed on NASDAQ or dealt in on any other recognised stock exchange on which the shares are listed.

73.2 To give effect to any sale of shares under this Article, the Board may authorise some person to transfer the shares in question and may enter the name of the transferee in respect of the transferred shares in the Register even if no share certificate has been lodged for such shares and may issue a new certificate to the transferee. An instrument of transfer executed by that person shall be as effective as if it had been executed by the holder of or the person entitled by transmission to, the shares. The buyer shall not be bound to see to the application of the purchase monies, nor shall his title to the shares be affected by any irregularity or invalidity in the proceedings in reference to the sale. If the shares are in uncertificated form, in accordance with the uncertificated securities rules, the Board may issue a written notification to the Operator requiring the conversion of the share to certificated form.

73.3 If during the period of 12 years referred to in Article 73.1, or during any period ending on the date when all the requirements of Articles 73.1(a) to 73.1(d) have been satisfied, any additional shares have been issued in respect of those held at the beginning of, or previously so issued during, any such period and all the requirements of Articles 73.1(b) to 73.1(d) have been satisfied in regard to such additional shares, the Company shall also be entitled to sell the additional shares.

74 **Application of Proceeds of Sale of Shares of Untraced Members**

The Company shall account to the member or other person entitled to the share for the net proceeds of a sale under Article 73 by carrying all monies relating to such sale to a separate account. The Company shall be deemed to be a debtor to, and not a trustee for, such member or other person in respect of such monies. Monies carried to such separate account may either be employed in the business of the Company or invested in such investments as the Board may think fit. No interest shall be payable to such member or other person in respect of such monies and the Company does not have to account for any money earned on them.

75 **Number of Directors**

Unless otherwise determined by the Company by ordinary resolution, the number of Directors (other than any alternate Directors) shall be at least two but shall not be subject to any maximum number.

76 **Power of Company to Appoint Directors**

Subject to these Articles and the Companies Acts, the Company may by ordinary resolution appoint a person who is willing to act to be a Director, either to fill a vacancy or as an addition to the existing Board but the total number of Directors shall not exceed any maximum number fixed in accordance with these Articles.

77 **Power of Board to Appoint Directors**

Subject to these Articles, the Board shall have power at any time to appoint any person who is willing to act as a Director, either to fill a vacancy or as an addition to the existing Board but the total number of Directors shall not exceed any maximum number fixed in accordance with these Articles.

78 **Eligibility of New Directors**

78.1 No person, other than a retiring Director (by rotation or otherwise), shall be appointed or re-appointed a Director at any general meeting unless:

(a) he is recommended by the Board; or

(b) at least seven but not more than 42 clear days before the date appointed for the meeting the Company has received notice from a member (other than the person proposed) entitled to vote at the meeting of his intention to propose a resolution for the appointment or re-appointment of that person, stating the particulars which would, if he were so appointed or re-appointed, be required to be included in the Company's register of directors and a notice executed by that person of his willingness to be appointed or re-appointed, is lodged at the Office.

78.2 A Director need not be a member of the Company.

79 **Classes and Retirement of Directors**

79.1 Following the Listing, the Directors shall be divided into three classes designated as “Class I”, “Class II” and “Class III”, respectively. The Board is authorised to assign members of the Board already in office such classes at the time the classification becomes effective.

79.2 At the first annual general meeting of the Company following the Listing, each Director in Class I shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.3 At the second annual general meeting of the Company following the Listing, each Director in Class II shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.4 At the third annual general meeting of the Company following the Listing, each Director in Class III shall retire from office but shall be eligible for re-appointment by ordinary resolution at such annual general meeting and, in each case, where such Director is so re-appointed, they shall be entitled to serve until the third anniversary of such annual general meeting of the Company, at which stage such Director shall retire from office but shall be eligible for further re-appointment.

79.5 At each succeeding annual general meeting of the Company following the third annual general meeting of the Company after the Listing, Directors shall be elected to serve for a term of three years to succeed the Directors of the class whose terms expire at such annual general meeting.

79.6 Notwithstanding the foregoing provisions, each Director shall serve until their successor is duly elected and qualified or until their earlier death, resignation or removal.

80 **Deemed Re-Appointment**

80.1 A Director who retires at an annual general meeting shall (unless he is removed from office or his office is vacated in accordance with these Articles) retain office until the close of the meeting at which he retires or (if earlier) when a resolution is passed at that meeting not to fill the vacancy or to elect another person in his place or the resolution to re-appoint him is put to the meeting and lost.

80.2 If the Company, at any meeting at which a Director retires in accordance with these Articles does not fill the office vacated by such Director, the retiring Director, if willing to act, shall be deemed to be re-appointed unless at that meeting a resolution is passed not to fill the vacancy or elect another person in his place or unless the resolution to re-appoint him is put to the meeting and lost.

81 **Procedure if Insufficient Directors Appointed**

81.1 If:

(a) at the annual general meeting in any year any resolution or resolutions for the appointment or re-appointment of the persons eligible for appointment or re appointment as Directors are put to the meeting and lost; and

(b) at the end of that meeting the number of Directors is fewer than any minimum number of Directors required under Article 75,

all retiring Directors who stood for re-appointment at that meeting (**Retiring Directors**) shall be deemed to have been re-appointed as Directors and shall remain in office but the Retiring Directors may only act for the purpose of filling vacancies, convening general meetings of the Company and performing such duties as are essential to maintain the Company as a going concern, and not for any other purpose.

81.2 The Retiring Directors shall convene a general meeting as soon as reasonably practicable following the meeting referred to in Article 81.1 and they shall retire from office at that meeting. If at the end of any meeting convened under this Article the number of Directors is fewer than any minimum number of Directors required under Article 75, the provisions of this Article shall also apply to that meeting.

82 **Removal of Directors**

In addition to any power of removal conferred by the Companies Acts, the Company may by special resolution, or by ordinary resolution of which special notice has been given in accordance with section 312 of the Act, remove a director before the expiry of his period of office (without prejudice to a claim for damages for breach of contract or otherwise) and may (subject to these Articles) by ordinary resolution appoint another person who is willing to act to be a director in his place.

83 **Vacation of Office by Director**

83.1 Without prejudice to the provisions for retirement (by rotation or otherwise) contained in these Articles, the office of a Director shall be vacated if:

(a) he resigns by notice in writing delivered to the Secretary at the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting;

(b) he offers to resign by notice in writing delivered to the Secretary at the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting and the Board resolves to accept such offer;

(c) he is requested to resign by all of the other Directors by notice in writing addressed to him at his address as shown in the register of Directors (without prejudice to any claim for damages which he may have for breach of any contract between him and the Company);

(d) he ceases to be a Director by virtue of any provision of the Companies Acts, is removed from office pursuant to these Articles or the Act or becomes prohibited by law from being a Director;

(e) he becomes bankrupt or makes an arrangement or composition with his creditors generally;

(f) a registered medical practitioner who is treating that person gives a written opinion to the Company stating that person has become physically or mentally incapable of acting as a director and may remain so for more than three months, or he is or has been suffering from mental or physical ill health and the Board resolves that his office be vacated; or

(g) he is absent (whether or not his alternate Director appointed by him attends), without the permission of the Board, from Board meetings for six consecutive months and a notice is served on him personally, or at his residential address provided to the Company under section 165 of the Act signed by all the other Directors stating that he shall cease to be a Director with immediate effect (and such notice may consist of several copies each signed by one or more Directors).

83.2 If the office of a Director is vacated for any reason, he shall cease to be a member of any committee or sub-committee of the Board.

84 **Resolution as to Vacancy Conclusive**

A resolution of the Board declaring a Director to have vacated office under the terms of Article 83 shall be conclusive as to the fact and ground of vacation stated in the resolution.

85 **Appointment of Alternate Directors**

85.1 Each Director may appoint any person (including another Director) to be his alternate and may at his discretion remove an alternate Director so appointed. Any appointment or removal of an alternate Director must be by written notice delivered to the Office or at an address specified by the Company for the purposes of communication by electronic means or tendered at a Board meeting or in any other manner approved by the Board. The appointment requires the approval of the Board unless it has been previously approved or the appointee is another Director.

85.2 An alternate Director must provide the particulars, and sign any form for public filing required by the Companies Acts relating to his appointment.

86 **Alternate Directors' Participation in Board Meetings**

86.1 Every alternate Director is (subject to his giving to the Company an address within the United Kingdom at which notices may be served on him (and, if applicable, an address in relation to which electronic communications may be received by him)) entitled to receive notice of all meetings of the Board and all committees of the Board of which his appointor is a member and, in his appointor's absence, to attend and vote at such meetings and to exercise all the powers, rights, duties and authorities of his appointor. Each person acting as an alternate Director shall have a separate vote at Board meetings for each Director for whom he acts as alternate Director in addition to his own vote if he is also a Director, but he shall count as only one for the purpose of determining whether a quorum is present.

86.2 Signature by an alternate Director of any resolution in writing of the Board or a committee of the Board will, unless the notice of his appointment provides otherwise, be as effective as signature by his appointor.

87 **Alternate Directors Responsible for Own Acts**

Each person acting as an alternate Director will be an officer of the Company, will alone be responsible to the Company for his own acts and defaults and will not be deemed to be the agent of the Director appointing him.

88 **Interests of Alternate Director**

An alternate Director is entitled to contract and be interested in and benefit from contracts or arrangements with the Company, to be repaid expenses and to be indemnified to the same extent as if he were a Director. However, he is not entitled to receive from the Company any fees for his services as alternate, except such part (if any) of the fee payable to his appointor as such appointor may by written notice to the Company direct.

89 **Revocation of Alternate Director**

An alternate Director will cease to be an alternate Director:

(a) if his appointor revokes his appointment; or

(b) if he resigns his office by notice in writing to the Company; or

(c) if his appointor ceases for any reason to be a Director, provided that if any Director retires but is re-appointed or deemed to be re-appointed at the same meeting, any valid appointment of an alternate Director which was in force immediately before his retirement shall remain in force; or

(d) if any event happens in relation to him which, if he were a Director otherwise appointed, would cause him to vacate his office.

90 **Directors' Fees**

Each of the Directors may be paid a fee at such rate as may from time to time be determined by the Board. However, the aggregate of all fees payable to the Directors (other than amounts payable under any other provision of these Articles) must not exceed £250,000 a year or such higher amount as may from time to time be decided by ordinary resolution of the Company. Any fees payable under this Article shall be distinct from any salary, remuneration or other amounts payable to a Director under any other provisions of these Articles and shall accrue from day to day.

91 **Expenses**

Each Director may be paid his reasonable travelling, hotel and other expenses properly incurred by him in or about the performance of his duties as Director, including any expenses incurred in attending meetings of the Board or any committee of the Board or general meetings or separate meetings of the holders of any class of shares or debentures of the Company. Subject to the Act, the Directors shall have the power to make arrangements to provide a Director with funds to meet expenditure incurred or to be incurred by him for the purposes of the Company or for the purpose of enabling him to perform his duties as an officer of the Company or to enable him to avoid incurring any such expenditure.

92 **Additional Remuneration**

If by arrangement with the Board any Director shall perform or render any special duties or services outside his ordinary duties as a Director and not in his capacity as a holder of employment or executive office, he may be paid such reasonable additional remuneration (whether by way of salary, commission, participation in profits or otherwise) as the Board may determine.

93 **Remuneration of Executive Directors**

The salary or remuneration of any Director appointed to hold any employment or executive office in accordance with these Articles may be either a fixed sum of money, or may altogether or in part be governed by business done or profits made or otherwise determined by the Board, and may be in addition to or instead of any fee payable to him for his services as Director under these Articles.

94 **Pensions and Other Benefits**

94.1 The Board may exercise all the powers of the Company to provide pensions or other retirement or superannuation benefits and to provide death or disability benefits or other allowances or gratuities (whether by insurance or otherwise) for any person who is or has at any time been a Director or employee of:

(a) the Company;

(b) any company which is or was a holding company or a subsidiary undertaking of the Company;

(c) any company which is or was allied to or associated with the Company or a subsidiary undertaking or holding company of the Company; or

(d) a predecessor in business of the Company or of any holding company or subsidiary undertaking of the Company,

and, in each case, for any member of his family (including a spouse or former spouse) and any person who is or was dependent on him.

94.2 The Board may establish, maintain, subscribe and contribute to any scheme, institution, association, club, trust or fund and pay premiums and, subject to the Companies Acts, lend money or make payments to, guarantee or give an indemnity in respect of, or give any financial or other assistance in connection with any of the matters set out in Article 94.1 above. The Board may procure any of such matters to be done by the Company either alone or in conjunction with any other person. Any Director or former Director shall be entitled to receive and retain for his own benefit any pension or other benefit provided under this Article and shall not have to account for it to the Company. The receipt of any such benefit will not disqualify any person from being or becoming a Director of the Company.

95 **Powers of the Board**

95.1 Subject to the Companies Acts, these Articles and to any directions given by special resolution of the Company, the business of the Company will be managed by the Board, which may exercise all the powers of the Company, whether relating to the management of the business or not.

95.2 No alteration of these Articles and no such direction given by the Company shall invalidate any prior act of the Board which would have been valid if such alteration had not been made or such direction had not been given. Provisions contained elsewhere in these Articles as to any specific power of the Board shall not be deemed to limit the general powers given by this Article.

96 **Powers of Directors if Less Than Minimum Number**

If the number of Directors is less than the minimum prescribed in Article 75 or decided by the Company by ordinary resolution, the remaining Director or Directors may act only for the purposes of appointing an additional Director or Directors to make up that minimum or convening a general meeting of the Company for the purpose of making such appointment. If no Director or Directors is or are able or willing to act, two members may convene a general meeting for the purpose of appointing Directors. An additional Director appointed in this way holds office (subject to these Articles) only until the dissolution of the next annual general meeting after his appointment unless he is reappointed during the annual general meeting.

97 **Powers of Executive Directors**

The Board or any committee authorised by the Board may:

(a) delegate or entrust to and confer on any Director holding executive office (including a chief executive or managing director, if appointed) such of its powers, authorities and discretions (with power to sub-delegate) for such time, on such terms and subject to such conditions as it thinks fit; and

(b) revoke, withdraw, alter or vary all or any of such powers.

98 **Delegation to Committees**

98.1 The Board may delegate any of its powers, authorities and discretions (with power to sub-delegate) for such time on such terms and subject to such conditions as it thinks fit to any committee consisting of one or more Directors and (if thought fit) one or more other persons provided that:

(a) a majority of the members of a committee shall be Directors; and

(b) no resolution of a committee shall be effective unless a majority of those present when it is passed are Directors or alternate Directors.

98.2 The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary any such powers and discharge any such committee in whole or in part. Insofar as any power, authority or discretion is so delegated, any reference in these Articles to the exercise by the Board of such power, authority or discretion shall be construed as if it were a reference to the exercise of such power, authority or discretion by such committee.

99 **Local Management**

99.1 The Board may establish any local or divisional boards or agencies for managing any of the affairs of the Company in any specified locality, either in the United Kingdom or elsewhere, and appoint any persons to be members of such local or divisional board, or any managers or agents, and may fix their remuneration.

99.2 The Board may delegate to any local or divisional board, manager or agent so appointed any of its powers, authorities and discretions (with power to sub-delegate) and may authorise the members of any such local or divisional board, or any of them, to fill any vacancies and to act notwithstanding vacancies. Any such appointment or delegation under this Article may be made, on such terms conditions as the Board may think fit. The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary all or any of such powers.

99.3 Subject to any terms and conditions expressly imposed by the Board, the proceedings of any local or divisional board or agency with two or more members shall be governed by such of these Articles as regulate the proceedings of the Board, so far as they are capable of applying.

100 **Board Meetings**

100.1 The Board can decide when and where to have meetings and how they will be conducted. They may also adjourn meetings.

100.2 A Board meeting can be called by any Director. The Secretary must call a Board meeting if asked to do so by a Director.

101 **Notice of Board Meetings**

101.1 Notice of a Board meeting shall be deemed to be duly given to a Director if it is given to him personally or by word of mouth or given in writing or by electronic means to him at his last known address or any other address given by him to the Company for that purpose.

101.2 A Director may waive the requirement that notice be given to him of any Board meeting, either prospectively or retrospectively and any retrospective waiver shall not affect the validity of the meeting or of any business conducted at the meeting.

101.3 It shall not be necessary to give notice of a Board meeting to a Director who is absent from the United Kingdom unless he has asked the Board in writing that notices of Board meetings shall during his absence be given to him at any address in the United Kingdom notified to the Company for this purpose, but he shall not, in such event, be entitled to a longer period of notice than if he had been present in the United Kingdom at that address.

102 **Quorum**

102.1 The quorum necessary for the transaction of business may be determined by the Board (but shall be no less than two persons) and until otherwise determined shall be two persons, each being a Director or an alternate Director. A duly convened meeting of the Board at which a quorum is present shall be competent to exercise all or any of the authorities, powers, and discretions for the time being vested in or exercisable by the Board.

102.2 If a Director ceases to be a director at a Board meeting, he can continue to be present and to act as a director and be counted in the quorum until the end of the meeting if no other Director objects and if otherwise a quorum of Directors would not be present.

103 **Chairman**

103.1 The Board may appoint one or more of its body as chairman or joint chairman and one or more of its body as deputy chairman of its meetings and may determine the period for which he is or they are to hold office and may at any time remove him or them from office.

103.2 If no such chairman or deputy chairman is elected, or if at any meeting neither a chairman nor a deputy chairman is present within ten minutes of the time appointed for holding the same, the Directors present shall choose one of their number to be chairman of such meeting. In the event two or more joint chairmen or, in the absence of a chairman, two or more deputy chairman being present, the joint chairman or deputy chairman to act as chairman of the meeting shall be decided by those Directors present.

104 **Voting**

Questions arising at any Board meeting shall be determined by a majority of votes. In the case of an equality of votes the chairman of that meeting shall have a second or casting vote (unless he is not entitled to vote on the resolution in question).

105 **Participation by Telephone or Other Form of Communication**

105.1 Any Director or his alternate may validly participate in a meeting of the Board or a committee of the Board through the medium of conference telephone or any other form of communications equipment (whether in use when these Articles are adopted or developed subsequently), provided that all persons participating in the meeting are able to hear and speak to each other throughout such meeting.

105.2 A person so participating by telephone or other communication shall be deemed to be present in person at the meeting and shall be counted in a quorum and entitled to vote. Such a meeting shall be deemed to take place where the largest group of those participating is assembled or, if there is no group which is larger than any other group, where the chairman of the meeting then is.

105.3 A resolution passed at any meeting held in the above manner, and signed by the chairman of the meeting, shall be as valid and effectual as if it had been passed at a meeting of the Board (or committee, as the case may be) duly convened and held.

106 **Resolution in Writing**

106.1 A resolution in writing signed or confirmed electronically by all the Directors for the time being entitled to receive notice of a Board meeting and to vote on the resolution and not being less than a quorum (or by all the members of a committee of the Board for the time being entitled to receive notice of such committee meeting and to vote on the resolution and not being less than a quorum of that committee), shall be as valid and effective for all purposes as a resolution duly passed at a meeting of the Board (or committee, as the case may be).

106.2 Such a resolution may consist of several documents or electronic communications in the same form each signed or authenticated by one or more of the Directors or members of the relevant committee.

107 **Proceedings of Committees**

All committees of the Board shall, in the exercise of the powers delegated to them and in the transaction of business, conform with any mode of proceedings and regulations which the Board may prescribe and subject to this shall be governed by such of these Articles as regulate the proceedings of the Board as are capable of applying.

108 **Minutes of Proceedings**

108.1 The Board shall keep minutes of all shareholder meetings, all Board meetings and meetings of committees of the Board. The minutes must include the names of the Directors present.

108.2 Any such minutes, if purporting to be signed by the chairman of the meeting at which the proceedings were held or by the chairman of the next meeting or the Secretary, shall be evidence of the matters stated in such minutes without any further proof.

109 **Validity of Proceedings**

All acts done by a meeting of the Board, or of a committee of the Board, or by any person acting as a Director, alternate Director or member of a committee shall be valid even if it is discovered afterwards that there was some defect in the appointment of any person or persons acting, or that they or any of them were or was disqualified from holding office or not entitled to vote, or had in any way vacated their or his office.

110 **Transactions or Other Arrangements With the Company**

110.1 Subject to the Companies Acts and provided he has declared the nature and extent of his interest in accordance with the requirements of the Companies Acts, a Director who is in any way, whether directly or indirectly, interested in an existing or proposed transaction or arrangement with the Company may:

(a) be a party to, or otherwise interested in, any transaction or arrangement with the Company or in which the Company is otherwise (directly or indirectly) interested;

(b) act by himself or through his firm in a professional capacity for the Company (otherwise than as auditor) and he or his firm shall be entitled to remuneration for professional services as if he were not a Director;

(c) be or become a director or other officer of, or employed by, or a party to a transaction or arrangement with, or otherwise interested in, any body corporate in which the Company is otherwise (directly or indirectly) interested; and

(d) hold any office or place of profit with the Company (except as auditor) in conjunction with his office of Director for such period and upon such terms, including as to remuneration as the Board may decide.

110.2 A Director shall not, save as he may otherwise agree, be accountable to the Company for any benefit which he derives from any such contract, transaction or arrangement or from any such office or employment or from any interest in any such body corporate and no such contract, transaction or arrangement shall be liable to be avoided on the grounds of any such interest or benefit nor shall the receipt of any such remuneration or other benefit constitute a breach of his duty under section 176 of the Act.

111 **Authorisation of Directors' Conflicts of Interest**

111.1 The Board may, in accordance with the requirements set out in this Article, authorise any matter or situation proposed to them by any Director which would, if not authorised, involve a Director (an **Interested Director**) breaching his duty under the Act to avoid conflicts of interest.

111.2 A Director seeking authorisation in respect of a conflict of interest shall declare to the Board the nature and extent of his interest in a conflict of interest as soon as is reasonably practicable. The Director shall provide the Board with such details of the matter as are necessary for the Board to decide how to address the conflict of interest together with such additional information as may be requested by the Board.

111.3 Any authorisation under this Article will be effective only if:

(a) to the extent permitted by the Act, the matter in question shall have been proposed by any Director for consideration in the same way that any other matter may be proposed to the Directors under the provisions of these Articles;

(b) any requirement as to the quorum for consideration of the relevant matter is met without counting the Interested Director and any other interested Director; and

(c) the matter is agreed to without the Interested Director voting or would be agreed to if the Interested Director's and any other interested Director's vote is not counted.

111.4 Any authorisation of a conflict of interest under this Article must be recorded in writing (but the authority shall be effective whether or not the terms are so recorded) and may (whether at the time of giving the authorisation or subsequently):

(a) extend to any actual or potential conflict of interest which may reasonably be expected to arise out of the matter or situation so authorised;

(b) provide that the Interested Director be excluded from the receipt of documents and information and the participation in discussions (whether at meetings of the Directors or otherwise) related to the conflict of interest;

(c) impose upon the Interested Director such other terms for the purposes of dealing with the conflict of interest as the Directors think fit;

(d) provide that, where the Interested Director obtains, or has obtained (through his involvement in the conflict of interest and otherwise than through his position as a Director) information that is confidential to a third party, he will not be obliged to disclose that information to the Company, or to use it in relation to the Company's affairs where to do so would amount to a breach of that confidence; and

(e) permit the Interested Director to absent himself from the discussion of matters relating to the conflict of interest at any meeting of the Directors and be excused from reviewing papers prepared by, or for, the Directors to the extent they relate to such matters.

111.5 Where the Directors authorise a conflict of interest, the Interested Director will be obliged to conduct himself in accordance with any terms and conditions imposed by the Directors in relation to the conflict of interest.

111.6 The Directors may revoke or vary such authorisation at any time, but this will not affect anything done by the Interested Director, prior to such revocation or variation, in accordance with the terms of such authorisation.

111.7 A Director is not required, by reason of being a Director (or because of the fiduciary relationship established by reason of being a director), to account to the Company for any remuneration, profit or other benefit which he derives from or in connection with a relationship involving a conflict of interest which has been authorised by the directors or by the Company in general meeting (subject in each case to any terms, limits or conditions attaching to that authorisation) and no contract shall be liable to be avoided on such grounds.

112 **Directors' Permitted Interests**

112.1 A Director cannot vote or be counted in the quorum on any resolution relating to any transaction or arrangement with the Company in which he has an interest and which may reasonably be regarded as likely to give rise to a conflict of interest but can vote (and be counted in the quorum) on the following:

(a) giving him any security, guarantee or indemnity for any money or any liability which he, or any other person, has lent or obligations he or any other person has undertaken at the request, or for the benefit, of the Company or any of its subsidiary undertakings;

(b) giving any security, guarantee or indemnity to any other person for a debt or obligation which is owed by the Company or any of its subsidiary undertakings, to that other person if the Director has taken responsibility for some or all of that debt or obligation. The Director can take this responsibility by giving a guarantee, indemnity or security;

(c) a proposal or contract relating to an offer of any shares or debentures or other securities for subscription or purchase by the Company or any of its subsidiary undertakings, if the Director takes part because he is a holder of shares, debentures or other securities, or if he takes part in the underwriting or sub underwriting of the offer;

(d) any arrangement for the benefit of employees of the Company or any of its subsidiary undertakings which only gives him benefits which are also generally given to employees to whom the arrangement relates;

(e) any arrangement involving any other company if the Director (together with any person connected with the Director) has an interest of any kind in that company (including an interest by holding any position in that company or by being a shareholder of that company). This does not apply if he knows that he has a Relevant Interest;

(f) a contract relating to insurance which the Company can buy or renew for the benefit of the Directors or a group of people which includes Directors; and

(g) a contract relating to a pension, superannuation or similar scheme or a retirement, death, disability benefits scheme or employees' share scheme which gives the Director benefits which are also generally given to the employees to whom the scheme relates.

112.2 A Director cannot vote or be counted in the quorum on a resolution relating to his own appointment or the settlement or variation of the terms of his appointment to an office or place of profit with the Company or any other company in which the Company has an interest.

112.3 Where the Directors are considering proposals about the appointment, or the settlement or variation of the terms or the termination of the appointment of two or more Directors to other offices or places of profit with the Company or any company in which the Company has an interest, a separate resolution may be put in relation to each Director and in that case each of the Directors concerned shall be entitled to vote and be counted in the quorum in respect of each resolution unless it concerns his own appointment or the settlement or variation of the terms or the termination of his own appointment or the appointment of another director to an office or place of profit with a company in which the Company has an interest and the Director seeking to vote or be counted in the quorum has a Relevant Interest in it.

112.4 A company shall be deemed to be one in which the Director has a **Relevant Interest** if and so long as (but only if and so long as) he is to his knowledge (either directly or indirectly) the holder of or beneficially interested in one per cent or more of any class of the equity share capital of that company (calculated exclusive of any shares of that class in that company held as treasury shares) or of the voting rights available to members of that company. In relation to an alternate Director, an interest of his appointor shall be treated as an interest of the alternate Director without prejudice to any interest which the alternate Director has otherwise. Where a company in which a Director has Relevant Interest is interested in a contract, he also shall be deemed interested in that contract.

112.5 If a question arises at a Board meeting about whether a Director (other than the chairman of the meeting) has an interest which is likely to give rise to a conflict of interest, or whether he can vote or be counted in the quorum, and the Director does not agree to abstain from voting on the issue or not to be counted in the quorum, the question must be referred to the chairman of the meeting. The chairman's ruling about the relevant Director is final and conclusive, unless the nature and extent of the Director's interests have not been fairly disclosed to the Directors. If the question arises about the chairman of the meeting, the question must be directed to the Directors. The chairman cannot vote on the question but can be counted in the quorum. The Directors' resolution about the chairman is final and conclusive, unless the nature and extent of the chairman's interests have not been fairly disclosed to the Directors.

113 **General**

113.1 For the purposes of Articles 110 to 112 inclusive (which shall apply equally to alternate Directors):

(a) An interest of a person who is connected (which word shall have the meaning given to it by section 252 of the Act) with a Director shall be treated as an interest of the Director.

(b) A contract includes references to any proposed contract and to any transaction or arrangement or proposed transaction or arrangement whether or not consulting a contract.

(c) A conflict of interest includes a conflict of interest and duty and a conflict of duties.

(d) Subject to the Companies Acts, the Company may by ordinary resolution suspend or relax the provisions of Articles 110 to 112 to any extent or ratify any contract not properly authorised by reason of a contravention of any of the provisions of Articles 110 to 112.

114 **Power of Attorney**

The Board may, by power of attorney or otherwise, appoint any person or persons to be the agent or attorney of the Company and may delegate to any such person or persons any of its powers, authorities and discretions (with power to sub-delegate), in each case for such purposes and for such time, on such terms (including as to remuneration) and conditions as it thinks fit. The Board may confer such powers either collaterally with, or to the exclusion of and in substitution for, all or any of the powers of the Board in that respect and may revoke, withdraw, alter or vary any of such powers.

115 **Exercise of Voting Power**

The Board may exercise or cause to be exercised the voting power conferred by the shares in any other company held or owned by the Company, or any power of appointment to be exercised by the Company, in such manner as it thinks fit (including the exercise of the voting power or power of appointment in favour of the appointment of any Director as a director or other officer or employee of such company or in favour of the payment of remuneration to the directors, officers or employees of such company).

116 **Provision for Employees on Cessation of Business**

The Board may, by resolution, sanction the exercise of the power to make provision for the benefit of persons employed or formerly employed by the Company or any of its subsidiary undertakings, in connection with the cessation or the transfer to any person of the whole or part of the undertaking of the Company or that subsidiary undertaking, but any such resolution shall not be sufficient for payments to or for the benefit of directors, former directors or shadow directors.

117 **Overseas Registers**

Subject to the Companies Acts, the Company may keep an overseas, local or other register and the Board may make and vary such regulations as it thinks fit respecting the keeping of any such register.

118 **Borrowing Powers**

118.1 Subject to these Articles and the Companies Acts, the Board may exercise all the powers of the Company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge all or any part of the undertaking, property and assets (present and future) and uncalled capital of the Company;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the Company or of any third party.

118.2 For the purpose of this Article, **Group** means the Company and its subsidiary undertakings for the time being.

118.3 Borrowings shall be deemed to include the following except in so far as otherwise taken into account:

(a) the nominal amount of any issued and paid up share capital (other than equity share capital) of any subsidiary undertaking of the Company owned otherwise than by a member of the Group;

(b) the nominal amount of any other issued and paid up share capital and the principal amount of any debentures or borrowed moneys which is not at the relevant time beneficially owned by a member of the Group, the redemption or repayment of which is the subject of a guarantee or indemnity by a member of the Group or which any member of the Group may be required to buy;

(c) the principal amount of any debenture (whether secured or unsecured) of a member of the Group beneficially owned otherwise than by a member of the Group;

(d) the outstanding amount raised by acceptances by any bank or accepting house under any acceptance credit opened by or on behalf of any member of the Group; and

(e) the minority proportion of moneys borrowed by a member of the Group and owing to a partly-owned subsidiary undertaking.

118.4 Borrowings shall not include and shall be deemed not to include:

(a) borrowings incurred by any member of the Group for the purpose of repaying within six months of the borrowing the whole or any part (with or without premium) of any borrowings of that or other member of the Group then outstanding, pending their application for such purpose within such period;

(b) the minority proportion of moneys borrowed by a partly owned subsidiary undertaking and not owing to another member of the Group.

118.5 When the aggregate principal amount of borrowings required to be taken into account on any particular date is being ascertained, any particular borrowing then outstanding which is denominated or repayable in a currency other than sterling shall be notionally converted into sterling at the rate of exchange prevailing in London on the last business day before that date or, if it would result in a lower figure, at the rate of exchange prevailing in London on the last business day six months before that date. For these purposes the rate of exchange shall be taken to be the spot rate in London recommended by a London clearing bank, selected by the Board, as being the most appropriate rate for the purchase by the company of the currency in question for sterling on the day in question.

118.6 A certificate or report by the auditors of the Company as to the amount of any borrowings or to the effect that the limit imposed by this Article has not been or will not be exceeded at any particular time or times, shall be conclusive evidence of such amount or fact for the purposes of this Article. Nevertheless the Board may at any time rely on a bona fide estimate of the aggregate of the borrowings. If, in consequence, the limit on borrowings set out in this Article is inadvertently exceeded, the amount of borrowings equal to the excess may be disregarded for 90 days after the date on which by reason of a determination of the auditors of the Company or otherwise the Board becomes aware that such a situation has or may have arisen.

118.7 No person dealing with the Company or any of its subsidiary undertakings shall be concerned to see or enquire whether the said limit is observed and no debt incurred or security given in excess of such limit shall be invalid or ineffectual unless the lender or recipient of the security had, at the time the debt was incurred or security given, express notice that the said limit had been or would be exceeded.

119 **Power to Authenticate Documents**

119.1 Any Director, the Secretary or any person appointed by the Board for the purpose shall have power to authenticate any documents affecting the constitution of the Company and any resolution passed by the Company or the Board or any committee, and any books, records, documents and accounts relating to the business of the Company, and to certify copies or extracts as true copies or extracts. Where any books, records, documents or accounts are not at the Office, the local manager or other officer of the Company who has their custody shall be deemed to be a person appointed by the Board for this purpose. A document purporting to be a copy of a resolution, or an extract from the minutes of a meeting, of the Company or the Board or any committee which is so certified shall be conclusive evidence in favour of all persons dealing with the Company that such resolution has been duly passed or, as the case may be, that any minute so extracted is a true and accurate record of proceedings at a duly constituted meeting.

120 **Use of Seals**

120.1 The Board shall provide for the safe custody of the Seal. A Seal shall not be used without the authority of the Board or of a committee of the Board so authorised.

120.2 Subject as otherwise provided in these Articles, every document which is sealed using the Seal must be signed by at least one authorised person in the presence of a witness who attests the signature. An authorised person for this purpose is any Director, the Secretary or any other person authorised by the Directors for the purpose of signing documents to which the Seal is applied.

120.3 The Seal shall be used only for sealing securities issued by the Company and documents creating or evidencing securities so issued. Any such securities or documents sealed with the Seal shall not require to be signed unless the Board decides otherwise or the law otherwise requires.

120.4 The Board may decide who will sign an instrument to which a Seal is affixed (or in the case of a share certificate, on which the Seal may be printed) either generally or in relation to a particular instrument or type of instrument and may also determine either generally or in a particular case that a signature may be dispensed with or affixed by mechanical means.

121 **Declaration of Dividends**

Subject to the Act and these Articles, the Company may by ordinary resolution declare dividends to be paid to members according to their respective rights and interests in the profits of the Company. However, no dividend shall exceed the amount recommended by the Board.

122 **Interim Dividends**

Subject to the Act, the Board may declare and pay such interim dividends (including any dividend at a fixed rate) as appears to the Board to be justified by the profits of the Company available for distribution. If the Board acts in good faith, it shall not incur any liability to the holders of shares for any loss that they may suffer by the lawful payment of any interim dividend on any other class of shares ranking with or after those shares.

123 **Calculation and Currency of Dividends**

Except as provided otherwise by the rights attached to shares, all dividends:

(a) shall be declared and paid accordingly to the amounts paid up (otherwise than in advance of calls) on the shares on which the dividend is paid;

(b) shall be apportioned and paid proportionately to the amounts paid up on the shares during any portion or portions of the period in respect of which the dividend is paid, but if any share is issued on terms that it shall rank for dividend as from a particular date, it shall rank for dividend accordingly; and

(c) may be declared or paid in any currency. The Board may decide the rate of exchange for any currency conversions that may be required and how any costs involved are to be met.

124 **Amounts Due on Shares can be Deducted from Dividends**

The Board may deduct from any dividend or other money payable to any person on or in respect of a share all such sums as may be due from him to the Company on account of calls or otherwise in relation to the shares of the Company. Sums so deducted can be used to pay amounts owing to the Company in respect of the shares.

125 **Dividends Not in Cash**

The Board may, by ordinary resolution of the Company direct, or in the case of an interim dividend may without the authority of an ordinary resolution direct, that payment of any dividend declared may be satisfied wholly or partly by the distribution of assets, and in particular of paid up shares or debentures of any other company, or in any one or more of such ways. Where any difficulty arises regarding such distribution, the Board may settle it as it thinks fit. In particular, the Board may:

(a) issue fractional certificates (or ignore fractions);

(b) fix the value for distribution of such assets or any part of them and determine that cash payments may be made to any members on the footing of the values so fixed, in order to adjust the rights of members; and

(c) vest any such assets in trustees on trust for the person entitled to the dividend.

126 **No Interest on Dividends**

Unless otherwise provided by the rights attached to the share, no dividend or other monies payable by the Company or in respect of a share shall bear interest as against the Company.

127 **Method of Payment**

127.1 The Company may pay any dividend, interest or other sum payable in respect of a share in cash or by direct debit, bank transfer, cheque, dividend warrant, or money order or by any other method, including by electronic means, as the Board may consider appropriate. For uncertificated shares, any payment may be made by means of the relevant system (subject always to the facilities and requirements of the relevant system) and such payment may be made by the Company or any person on its behalf by sending an instruction to the operator of the relevant system to credit the cash memorandum account of the holder or joint holders of such shares or, if permitted by the Company, of such person as the holder or joint holders may in writing direct.

127.2 The Company may send such payment by post or other delivery service (or by such means offered by the Company as the member or person entitled to it may agree in writing) to the registered address of the member or person entitled to it (or, if two or more persons are holders of the share or are jointly entitled to it because of the death or bankruptcy of the member or otherwise by operation of law, to the registered address of such of those persons as is first named in the Register) or to such person and such address as such member or person may direct in writing.

127.3 Every cheque, warrant, order or other form of payment is sent at the risk of the person entitled to the money represented by it, shall be made payable to the person or persons entitled, or to such other person as the person or persons entitled may direct in writing. Payment of the cheque, warrant, order or other form of payment (including transmission of funds through a bank transfer or other funds transfer system or by such other electronic means as permitted by these Articles or in accordance with the facilities and requirements of the relevant system concerned) shall be good discharge to the Company. If any such cheque, warrant, order or other form of payment has or shall be alleged to have been lost, stolen or destroyed the Company shall not be responsible.

127.4 Any joint holder or other person jointly entitled to a share may give an effective receipt for any dividend or other monies payable in respect of such share.

127.5 The Board may, at its discretion, make provisions to enable any member as the Board shall determine to receive duly declared dividends in a currency or currencies other than sterling. For the purposes of the calculation of the amount receivable in respect of any dividend, the rate of exchange to be used to determine the foreign currency equivalent of any sum payable as a dividend shall be such rate or rates and the payment shall be on such terms and conditions as the Board may in its absolute discretion determine.

128 **Uncashed Dividends**

If cheques, warrants or orders for dividends or other sums payable in respect of a share sent by the Company to the person entitled to them are returned to the Company or left uncashed on two consecutive occasions or, following one occasion, reasonable enquires have failed to establish any new address to be used for the purpose, the Company does not have to send any dividends or other monies payable in respect of that share due to that person until he notifies the Company of an address to be used for the purpose.

129 **Unclaimed Dividends**

All dividends, interest or other sums payable and unclaimed for 12 months after having become payable may be invested or otherwise made use of by the Board for the benefit of the Company until claimed. The Company shall not be a trustee in respect of such unclaimed dividends and will not be liable to pay interest on it. All dividends that remain unclaimed for 12 years after they were first declared or became due for payment shall (if the Board so resolves) be forfeited and shall cease to remain owing by the Company.

130 **Scrip Dividends**

Subject to the Act, the Board may, by ordinary resolution of the Company and subject to such terms and conditions as the Board may determine, offer to any holders of ordinary shares (excluding any member holding shares as treasury shares) the right to elect to receive ordinary shares, credited as fully paid, instead of cash in respect of the whole (or some part, to be determined by the Board) of any dividend specified by the ordinary resolution. The following provisions shall apply:

(a) the said resolution may specify a particular dividend, or may specify all or any dividends declared within a specified period or periods but such period may not end later than the fifth anniversary of the date of the meeting at which the ordinary resolution is passed;

(b) the entitlement of each holder of ordinary shares to new ordinary shares shall be such that the relevant value of the entitlement shall be as nearly as possible equal to (but not greater than) the cash amount (disregarding any tax credit) of the dividend that such holder would have received by way of dividend. For this purpose **relevant value** shall be calculated by reference to the average of the middle market quotations for the ordinary shares, certificated or uncertificated depositary instruments in respect of such shares, on NASDAQ (or any other publication of a recognised investment exchange showing quotations for the Company's ordinary shares), for the day on which the ordinary shares are first quoted "ex" the relevant dividend and the four subsequent dealing days, or in such other manner as the Board may determine on such basis as it considers to be fair and reasonable. A certificate or report by the Company's auditors as to the amount of the relevant value in respect of any dividend shall be conclusive evidence of that amount;

(c) no fractions of a share shall be allotted. The Board may make such provisions as it thinks fit for any fractional entitlements including provisions where, in whole or in part, the benefit accrues to the Company and/or under which fractional entitlements are accrued and/or retained and in each case accumulated on behalf of any member and such accruals or retentions are applied to the allotment by way of bonus to or cash subscription on behalf of any member of fully paid ordinary shares and/or provisions where cash payments may be made to members in respect of their fractional entitlements;

(d) the Board shall, after determining the basis of allotment, notify the holders of ordinary shares in writing of the right of election offered to them, and specify the procedure to be followed and place at which, and the latest time by which, elections must be lodged in order to be effective. No such notice need to be given to holders of ordinary shares who have previously given election mandates in accordance with this Article

and whose mandates have not been revoked. The accidental omission to give notice of any right of election to, or the non-receipt (even if the Company becomes aware of such non-receipt) of any such notice by, any holder of ordinary shares entitled to the same shall neither invalidate any offer of an election nor give rise to any claim, suit or action;

(e) the Board shall not proceed with any election unless the company has sufficient reserves or funds that may be capitalised, and the Board has authority to allot sufficient shares, to give effect to it after the basis of the allotment is determined;

(f) the Board may exclude from any offer or make other arrangements in relation to any holders of ordinary shares where the Board considers that the making of the offer to them or in respect of such shares would or might involve the contravention of the laws of any territory or that for any other reason the offer should not be made to them or in respect of such shares;

(g) the Board may establish or vary a procedure for election mandates in respect of future rights of election and may determine that every duly effected election in respect of any ordinary shares shall be binding on every successor in title to the holder;

(h) the dividend (or that part of the dividend in respect of which a right of election has been offered) shall not be payable on ordinary shares in respect of which an election has been duly made (**elected ordinary shares**) and instead additional ordinary shares shall be allotted to the holders of the elected ordinary shares on the basis of allotment determined as stated above. For such purpose the Board may capitalise, out of any amount for the time being standing to the credit of any reserve or fund (including any share premium account or capital redemption reserve) or of any of the profits which could otherwise have been applied in paying dividends in cash as the Board may determine, a sum equal to the aggregate nominal amount of the additional ordinary shares to be allotted on such basis and apply it in paying up in full the appropriate number of unissued ordinary shares for allotment and distribution to the holders of the elected ordinary shares on such basis. The Board may do all acts and things considered necessary or expedient to give effect to any such capitalisation;

(i) the Board may decide how any costs relating to the new shares available in place of a cash dividend will be met, including to deduct an amount from the entitlement of a holder of ordinary shares under this Article;

(j) the additional ordinary shares so allotted shall rank pari passu in all respects with each other and with the fully paid ordinary shares in issue on the record date for the dividend in respect of which the right of election has been offered, except that they will not rank for any dividend or other distribution or other entitlement which has been declared, paid or made by reference to such record date; and

(k) the Board may terminate, suspend, or amend any offer of the right to elect to receive ordinary shares in lieu of any cash dividend at any time and generally may implement any scrip dividend scheme on such terms and conditions as the Board may determine and take such other action as the Board may deem necessary or desirable in respect of any such scheme.

131 **Capitalisation of Reserves**

131.1 The Board may, with the authority of an ordinary resolution of the Company:

(a) subject as provided in this Article, resolve to capitalise any undivided profits of the Company not required for paying any preferential dividend (whether or not they are available for distribution) or any sum standing to the credit of any reserve or fund of the Company which is available for distribution or standing to the credit of the share premium account of capital redemption reserve or other undistributable reserve;

(b) appropriate the sum resolved to be capitalised to the members in proportion to the nominal amounts of the shares (whether or not fully paid) held by them respectively which would entitle them to participate in a distribution of that sum if the shares were fully paid and the sum were then distributable and were distributed by way of dividend and apply such sum on their behalf either in or towards paying up the amounts, if any, for the time being unpaid on any shares held by them respectively, or in paying up in full unissued shares or debentures of the Company of a nominal amount equal to that sum, and allot the shares or debentures credited as fully paid to those members or as they may direct, in those proportions, or partly in one way and partly in the other, provided that:

(i) the share premium account, the capital redemption reserve, any other undistributable reserve and any profits which are not available for distribution may, for the purposes of this Article, only be applied in paying up in full shares to be allotted to members credited as fully paid;

(ii) the Company will also be entitled to participate in the relevant distribution in relation to any shares of the relevant class held by it as treasury shares and the proportionate entitlement of the relevant class of members to the distribution will be calculated accordingly; and

(iii) in a case where any sum is applied in paying amounts for the time being unpaid on any shares of the Company or in paying up in full debentures of the Company, the amount of the net assets of the Company at that time in not less than the aggregate of the called up share capital of the Company and its undistributable reserves as shown in the latest audited accounts of the Company or such other accounts as may be relevant and would not be reduced below that aggregate by the payment of it;

(c) resolve that any shares so allotted to any member in respect of a holding by him of any partly paid shares shall, so long as such shares remain partly paid, rank for dividends only to the extent that such partly paid shares rank for dividends;

(d) make such provision by the issue of fractional certificates (or by ignoring fractions or by accruing the benefit of it to the Company rather than to the members concerned) or by payment in cash or otherwise as it thinks fit in the case of shares or debentures becoming distributable in fractions;

(e) authorise any person to enter on behalf of such members concerned into an agreement with the Company providing for either:

(i) the allotment to them respectively, credited as fully paid up, of any shares or debentures to which they may be entitled on such capitalisation; or

(ii) the payment up by the Company on behalf of such members by the application of their respective proportions of the reserves or profits resolved to be capitalised, of the amounts or any part of the amounts remaining unpaid on their existing shares,

(any agreement made under such authority being effective and binding on all such members); and

(f) generally do all acts and things required to give effect to such resolution.

132 **Record Dates**

132.1 Notwithstanding any other provision of these Articles but without prejudice to the rights attached to any shares and subject always to the Act, the Company or the Board may by resolution specify any date (**record date**) as the date at the close of business (or such other time as the Board may determine) on which persons registered as the holders of shares or other securities shall be entitled to receipt of any dividend, distribution, interest, allotment, issue, notice, information, document or circular. Such record date may be before, on or after the date on which the dividend, distribution, interest, allotment, issue, notice, information, document or circular is declared, made, paid, given, or served.

132.2 In the absence of a record date being fixed, entitlement to any dividend, distribution, interest, allotment, issue, notice, information, document or circular shall be determined by reference to the date on which the dividend is declared, the distribution allotment or issue is made or the notice, information, document or circular made, given or served.

133 **Inspection of Records**

No member (other than a Director) shall have any right to inspect any accounting record or other document of the Company unless he is authorised to do so by law, by order of a court of competent jurisdiction, by the Board or by ordinary resolution of the Company.

134 **Accounts to be Sent to Members**

134.1 In respect of each financial year, a copy of the Company's annual accounts, the strategic report, the Directors' report, the Directors' remuneration report, the auditor's report on those accounts and on the auditable part of the Directors' remuneration report shall be sent or supplied to:

(a) every member (whether or not entitled to receive notices of general meetings);

(b) every holder of debentures (whether or not entitled to receive notice of general meetings); and

(c) every other person who is entitled to receive notice of general meetings;

not less than 21 clear days before the date of the meeting at which copies of those documents are to be laid in accordance with the Act.

134.2 This Article does not require copies of the documents to which it applies to be sent or supplied to:

(a) a member or holder of debentures of whose address the Company is unaware; or

(b) more than one of the joint holders of shares or debentures.

134.3 The Board may determine that persons entitled to receive a copy of the Company's annual accounts, the strategic report, the Directors' report, the Directors' remuneration report, the auditor's report on those accounts and on the auditable part of the Directors' remuneration report are those persons entered on the Register at the close of business on a day determined by the Board, provided that the day determined by the Board may not be more than 21 days before the day that the relevant copies are being sent.

134.4 Where permitted by the Act, a strategic report with supplementary material in the form and containing the information prescribed by the Act may be sent or supplied to a person so electing in place of the documents required to be sent or supplied by Article 134.1.

135 **Service of Notices**

135.1 The Company can send, deliver or serve any notice or other document, including a share certificate, to or on a member:

(a) personally;

(b) by sending it through the postal system addressed to the member at his registered address or by leaving it at that address addressed to the member;

(c) through a relevant system, where the notice or document relates to uncertificated shares;

(d) where appropriate, by sending or supplying it in electronic form to an address notified by the member to the Company for that purpose;

(e) where appropriate, by making it available on a website and notifying the member of its availability in accordance with this Article; or

(f) by any other means authorised in writing by the member.

135.2 In the case of joint holders of a share:

(a) service, sending or supply of any notice, document or other information on or to one of the joint holders shall for all purposes be deemed a sufficient service on, sending or supplying to all the joint holders; and

(b) anything to be agreed or specified in relation to any notice, document or other information to be served on, sent or supplied to them may be agreed or specified by any one of the joint holders and the agreement or specification of the first named in the Register shall be accepted to the exclusion of that of the other joint holders.

135.3 Where a member (or, in the case of a joint holders, the person first named in the Register) has a registered address outside the United Kingdom but has notified the Company of an address within the United Kingdom at which notices, documents or other information may be given to him or has given to the Company an address for the purposes of communications by electronic means at which notices, documents or other information may be served, sent or supplied to him, he shall be entitled to have notices served, sent or supplied to him at such address or, where applicable, the Company may make them available on a website and notify the holder of that address. Otherwise no such member shall be entitled to receive any notice, document or other information from the Company.

135.4 If on three consecutive occasions any notice, document or other information has been sent to any member at his registered address or his address for the service of notices (by electronic means or otherwise) but has been returned undelivered, such member shall not be entitled to receive notices, documents or other information from the Company until he shall have communicated with the Company and supplied in writing a new registered address or address within the United Kingdom for the service of notices or has informed the Company of an address for the service of notices and the sending or supply of documents and other information in electronic form. For these purposes, any notice, document or other information served, sent or supplied by post shall be treated as returned undelivered if the notice, document or other information is served, sent or supplied back to the Company (or its agents) and a notice, document or other information served, sent or supplied in electronic form shall be treated as returned undelivered if the Company (or its agents) receives notification that the notice, document or other information was not delivered to the address to which it was served, sent or supplied.

135.5 The Company may at any time and in its sole discretion choose to serve, send or supply notices, documents or other information in hard copy form alone to some or all of the members.

136 **Notice on Person Entitled By Transmission**

The Company may give notice to the person entitled to a share because of the death or bankruptcy of a member or otherwise by operation of law, by sending or delivering it in any manner authorised by these Articles for the giving of notice to a member, addressed to that person by name, or by the title of representative of the deceased or trustee of the bankrupt or representative by operation of law or by any like description, at the address (if any) within the United Kingdom supplied for the purpose by the person claimed to be so entitled or to which notices may be sent in electronic form. Until such an address has been so supplied, a notice may be given in any manner in which it might have been given if the death or bankruptcy or operation of law had not occurred.

137 **Record Date for Service**

Any notice, document or other information may be served, sent or supplied by the Company by reference to the register as it stands at any time not more than 15 days before the date of service, sending or supplying. No change in the register after that time shall invalidate that service, sending or supply. Where any notice, document or other information is served on, sent or supplied to any person in respect of a share in accordance with these Articles, no person deriving any title or interest in that share shall be entitled to any further service, sending or supplying of that notice, document or other information.

138 **Evidence of Service**

138.1 Any notice, document or other information, addressed to a member at his registered address or address for service in the United Kingdom shall, if served, sent or supplied by first class post, be deemed to have been served or delivered on the day after the day when it was put in the post (or, where second class post is employed, on the second day after the day when it was put in the post). Proof that an envelope containing the notice, document or other information was properly addressed and put into the post as a prepaid letter shall be conclusive evidence that the notice was given.

138.2 Any notice, document or other information not served, sent or supplied by post but delivered or left at a registered address or address for service in the United Kingdom (other than an address for the purposes of communications by electronic means) shall be deemed to have been served or delivered on the day on which it was so delivered or left.

138.3 Any notice, document or other information, if served, sent or supplied by electronic means shall be deemed to have been received on the day on which the electronic communication was sent by or on behalf of the Company notwithstanding that the Company subsequently sends a hard copy of such notice, document or other information by post. Any notice, document or other information made available on a website shall be deemed to have been received on the day on which the notice, document or other information was first made available on the website or, if later, when a notice of availability is received or deemed to have been received pursuant to this Article. Proof that the notice, document or other information was properly addressed shall be conclusive evidence that the notice by electronic means was given.

138.4 Any notice, document or other information served, sent or supplied by the Company by means of a relevant system shall be deemed to have been received when the Company or any sponsoring system-participant acting on its behalf sends the issuer-instruction relating to the notice, document or other information.

138.5 Any notice, document or other information served, sent or supplied by the Company by any other means authorised in writing by the member concerned shall be deemed to have been received when the Company has carried out the action it has been authorised to take for that purpose.

139 **Notice When Post not Available**

If at any time by reason of the suspension, interruption or curtailment of postal services within the United Kingdom the Company is unable effectively to convene a general meeting by notices sent through the post, the Company need only give notice of a general meeting to those members with whom the Company can communicate by electronic means and who have provided the Company with an address for this purpose. The Company shall also advertise the notice in at least one national newspaper published in the United Kingdom and make it available on its website from the date of such advertisement until the conclusion of the meeting or any adjournment of it. In any such case the Company shall send confirmatory copies of the notice by post to those members to whom notice cannot be given by electronic means if, at least seven days prior to the meeting, the posting of notices to addresses throughout the United Kingdom again becomes practicable.

140 **Indemnity and Insurance**

140.1 In this Article:

(a) companies are **associated** if one is a subsidiary of the other or both are subsidiaries of the same body corporate;

(b) a **relevant officer** means any Director or other officer or former director or other officer of the Company or an associated company (including any company which is a trustee of an occupational pension scheme (as defined by section 235(6) of the Act), but excluding in each case any person engaged by the Company (or associated company) as auditor (whether or not he is also a director or other officer), to the extent he acts in his capacity as auditor); and

(c) **relevant loss** means any loss or liability which has been or may be incurred by a relevant officer in connection with that relevant officer's duties or powers in relation to the company, any associated company or any pension fund or employees' share scheme of the company or associated company.

140.2 Subject to Article 140.4, but without prejudice to any indemnity to which a relevant officer is otherwise entitled:

(a) each relevant officer shall be indemnified out of the Company's assets against all relevant loss and in relation to the Company's (or any associated company's) activities as trustee of an occupational pension scheme (as defined in section 235(6) of the Act), including any liability incurred by him in defending any civil or criminal proceedings, in which judgment is given in his favour or in which he is acquitted or the proceedings are otherwise disposed of without any finding or admission of any material breach of duty on his part or in connection with any application in which the court grants him, in his capacity as a relevant officer, relief from liability for negligence, default, breach of duty or breach of trust in relation to the Company's (or any associated company's) affairs; and

(b) the Company may provide any relevant officer with funds to meet expenditure incurred or to be incurred by him in connection with any proceedings or application referred to in Article 140.2(a) and otherwise may take any action to enable any such relevant officer to avoid incurring such expenditure.

140.3 This Article does not authorise any indemnity which would be prohibited or rendered void by any provision of the Companies Acts or by any other provision of law.

140.4 The Directors may decide to purchase and maintain insurance, at the expense of the Company, for the benefit of any relevant officer in respect of any relevant loss.

Exhibit 2.1

DEPOSIT AGREEMENT

by and among

ORCHARD THERAPEUTICS PLC

and

CITIBANK, N.A.,
as Depositary,

and

THE HOLDERS AND BENEFICIAL OWNERS OF
AMERICAN DEPOSITARY SHARES
ISSUED HEREUNDER

Dated as of November 2, 2018

TABLE OF CONTENTS

DEPOSIT AGREEMENT

DEPOSIT AGREEMENT, dated as of November 2, 2018, by and among (i) Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales, and its successors (the "Company"), (ii) CITIBANK, N.A., a national banking association organized under the laws of the United States of America ("Citibank") acting in its capacity as depositary, and any successor depositary hereunder (Citibank in such capacity, the "Depositary"), and (iii) all Holders and Beneficial Owners of American Depositary Shares issued hereunder (all such capitalized terms as hereinafter defined).

W I T N E S S E T H T H A T:

WHEREAS, the Company desires to establish with the Depositary an ADR facility to provide for the deposit of the Shares (as hereinafter defined) and the creation of American Depositary Shares representing the Shares so deposited and for the execution and Delivery (as hereinafter defined) of American Depositary Receipts (as hereinafter defined) evidencing such American Depositary Shares; and

WHEREAS, the Depositary is willing to act as the Depositary for such ADR facility upon the terms set forth in the Deposit Agreement (as hereinafter defined); and

WHEREAS, any American Depositary Receipts issued pursuant to the terms of the Deposit Agreement are to be substantially in the form of Exhibit A attached hereto, with appropriate insertions, modifications and omissions, as hereinafter provided in the Deposit Agreement; and

WHEREAS, the Board of Directors of the Company (or an authorized committee thereof) has duly approved the establishment of an ADR facility upon the terms set forth in the Deposit Agreement, the execution and delivery of the Deposit Agreement on behalf of the Company, and the actions of the Company and the transactions contemplated herein.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the parties hereto agree as follows:

ARTICLE I

DEFINITIONS

All capitalized terms used, but not otherwise defined, herein shall have the meanings set forth below, unless otherwise clearly indicated:

Section 1.1 **"ADS Record Date"** shall have the meaning given to such term in Section 4.9.

Section 1.2 **"Affiliate"** shall have the meaning assigned to such term by the Commission (as hereinafter defined) under Regulation C promulgated under the Securities Act (as hereinafter defined), or under any successor regulation thereto.

Section 1.3 "**American Depositary Receipt(s)", "ADR(s)" and "Receipt(s)**"shall mean the certificate(s) issued by the Depositary to evidence the American Depositary Shares issued under the terms of the Deposit Agreement in the form of Certificated ADS(s) (as hereinafter defined), as such ADRs may be amended from time to time in accordance with the provisions of the Deposit Agreement. An ADR may evidence any number of ADSs and may, in the case of ADSs held through a central depository such as DTC, be in the form of a "Balance Certificate."

Section 1.4 **"American Depositary Share(s)" and "ADS(s)"**shall mean the rights and interests in the Deposited Property (as hereinafter defined) granted to the Holders and Beneficial Owners pursuant to the terms and conditions of the Deposit Agreement and, if issued as Certificated ADS(s) (as hereinafter defined), the ADR(s) issued to evidence such ADSs. ADS(s) may be issued under the terms of the Deposit Agreement in the form of (a) Certificated ADS(s) (as hereinafter defined), in which case the ADS(s) are evidenced by ADR(s), or (b) Uncertificated ADS(s) (as hereinafter defined), in which case the ADS(s) are not evidenced by ADR(s) but are reflected on the direct registration system maintained by the Depositary for such purposes under the terms of Section 2.13. Unless otherwise specified in the Deposit Agreement or in any ADR, or unless the context otherwise requires, any reference to ADS(s) shall include Certificated ADS(s) and Uncertificated ADS(s), individually or collectively, as the context may require. Each ADS shall represent the right to receive, and to exercise the beneficial ownership interests in, the number of Shares specified in the form of ADR attached hereto as Exhibit A (as amended from time to time) that are on deposit with the Depositary and/or the Custodian, subject, in each case, to the terms and conditions of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS), until there shall occur a distribution upon Deposited Securities referred to in Section 4.2 or a change in Deposited Securities referred to in Section 4.11 with respect to which additional ADSs are not issued, and thereafter each ADS shall represent the right to receive, and to exercise the beneficial ownership interests in, the applicable Deposited Property on deposit with the Depositary and the Custodian determined in accordance with the terms of such Sections, subject, in each case, to the terms and conditions of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS). In addition, the ADS(s)-to-Share(s) ratio is subject to amendment as provided in Article IV of the Deposit Agreement (which may give rise to Depositary fees).

Section 1.5 **"Applicant"**shall have the meaning given to such term in Section 5.10.

Section 1.6 **"Articles of Association"**shall mean the Articles of Association of the Company, as amended and restated from time to time.

Section 1.7 **"Beneficial Owner"** shall mean, as to any ADS, any person or entity having a beneficial interest deriving from the ownership of such ADS. Notwithstanding anything else contained in the Deposit Agreement, any ADR(s) or any other instruments or agreements relating to the ADSs and the corresponding Deposited Property, the Depositary, the Custodian and their respective nominees are intended to be, and shall at all times during the term of the Deposit Agreement be, the record holders only of the Deposited Property represented by the ADSs for the benefit of the Holders and Beneficial Owners of the corresponding ADSs. The Depositary, on its own behalf and on behalf of the Custodian and their respective nominees, disclaims any beneficial ownership interest in the Deposited Property held on behalf of the Holders and Beneficial Owners of ADSs. The beneficial ownership interests in the Deposited Property are intended to be, and shall at all times during the term of the Deposit Agreement continue to be, vested in the Beneficial Owners of the ADSs representing the Deposited Property. The beneficial ownership interests in the Deposited Property shall, unless otherwise agreed by the Depositary, be exercisable by the Beneficial Owners of the ADSs only through the Holders of such ADSs, by the Holders of the ADSs (on behalf of the applicable Beneficial Owners) only through the Depositary, and by the Depositary (on behalf of the Holders and Beneficial Owners of the corresponding ADSs) directly, or indirectly through the Custodian or their respective nominees, in each case upon the terms of the Deposit Agreement and, if applicable, the terms of the ADR(s) evidencing the ADSs. A Beneficial Owner of ADSs may or may not be the Holder of such ADSs. A Beneficial Owner shall be able to exercise any right or receive any benefit hereunder solely through the person who is the Holder of the ADSs owned by such Beneficial Owner. Unless otherwise identified to the Depositary, a Holder shall be deemed to be the Beneficial Owner of all the ADSs registered in his/her/its name. The manner in which a Beneficial Owner holds ADSs (e.g., in a brokerage account vs. as registered holder) may affect the rights and obligations of, the manner in which, and the extent to which, services are made available to, Beneficial Owners pursuant to the terms of the Deposit Agreement.

Section 1.8 **"Certificated ADS(s)"** shall have the meaning set forth in Section 2.13.

Section 1.9 **"Citibank"** shall mean Citibank, N.A., a national banking association organized under the laws of the United States of America, and its successors.

Section 1.10 **"Commission"** shall mean the Securities and Exchange Commission of the United States or any successor governmental agency thereto in the United States.

Section 1.11 **"Company"** shall mean Orchard Therapeutics plc, a public limited company incorporated and existing under the laws of England and Wales, and its successors.

Section 1.12 **"CREST"** shall mean the system for the paperless settlement of trades in securities and the holding of uncertificated securities operated by Euroclear UK & Ireland Limited in accordance with the Uncertificated Securities Regulations 2001 (SI 2001 No. 3755), as amended from time to time, or any successor thereto.

Section 1.13 **"Custodian"** shall mean (i) as of the date hereof, Citibank, N.A. (London), having its principal office at 25 Canada Square, Canary Wharf, London, E14 5LB, United Kingdom, as the custodian of Deposited Property for the purposes of the Deposit Agreement, (ii) Citibank, N.A., acting as custodian of Deposited Property pursuant to the Deposit Agreement, and (iii) any other entity that may be appointed by the Depositary pursuant to the terms of Section 5.5 as successor, substitute or additional custodian hereunder. The term "Custodian" shall mean any Custodian individually or all Custodians collectively, as the context requires.

Section 1.14 **"Deliver" and "Delivery"** shall mean (x) *when used in respect of Shares and other Deposited Securities*, whichever is appropriate of (i) the physical delivery of the certificate(s) representing such securities, or (ii) the book-entry transfer and recordation of such securities on the books of the Share Registrar (as hereinafter defined) or in the book-entry settlement of CREST, and (y) *when used in respect of ADSs*, either (i) the physical delivery of ADR(s) evidencing the ADSs, or (ii) the book-entry transfer and recordation of ADSs on the books of the Depositary or any book-entry settlement system in which the ADSs are settlement-eligible.

Section 1.15 **"Deposit Agreement"** shall mean this Deposit Agreement and all exhibits hereto, as the same may from time to time be amended and supplemented from time to time in accordance with the terms of the Deposit Agreement.

Section 1.16 "**Depositary**" shall mean Citibank, N.A., a national banking association organized under the laws of the United States, in its capacity as depositary under the terms of the Deposit Agreement, and any successor depositary hereunder.

Section 1.17 **"Deposited Property"** shall mean the Deposited Securities and any cash and other property held on deposit by the Depositary and the Custodian in respect of the ADSs or the Deposited Securities under the terms of the Deposit Agreement, subject, in the case of cash, to the provisions of Section 4.8. All Deposited Property shall be held by the Custodian, the Depositary and their respective nominees for the benefit of the Holders and Beneficial Owners of the ADSs representing the Deposited Property. The Deposited Property is not intended to, and shall not, constitute proprietary assets of the Depositary, the Custodian or their nominees. Beneficial ownership in the Deposited Property is intended to be, and shall at all times during the term of the Deposit Agreement continue to be, vested in the Beneficial Owners of the ADSs representing the Deposited Property.

Section 1.18 **"Deposited Securities"** shall mean the Shares and any other securities held on deposit by the Custodian from time to time in respect of the ADSs under the Deposit Agreement and constituting Deposited Property.

Section 1.19 **"Dollars" and "$"** shall refer to the lawful currency of the United States.

Section 1.20 **"DTC"** shall mean The Depository Trust Company, a national clearinghouse and the central book-entry settlement system for securities traded in the United States and, as such, the custodian for the securities of DTC Participants (as hereinafter defined) maintained in DTC, and any successor thereto.

Section 1.21 **"DTC Participant"** shall mean any financial institution (or any nominee of such institution) having one or more participant accounts with DTC for receiving, holding and delivering the securities and cash held in DTC. A DTC Participant may or may not be a Beneficial Owner. If a DTC Participant is not the Beneficial Owner of the ADSs credited to its account at DTC, or of the ADSs in respect of which the DTC Participant is otherwise acting, such DTC Participant shall be deemed, for all purposes hereunder, to have all requisite authority to act on behalf of the Beneficial Owner(s) of the ADSs credited to its account at DTC or in respect of which the DTC Participant is so acting. A DTC Participant, upon acceptance in any one of its DTC accounts of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement, shall (notwithstanding any explicit or implicit disclosure that it may be acting on behalf of another party) be deemed for all purposes to be a party to, and bound by, the terms of the Deposit Agreement and the applicable ADR(s) to the same extent as, and as if the DTC Participant were, the Holder of such ADSs.

Section 1.22 **"Exchange Act"** shall mean the United States Securities Exchange Act of 1934, as amended from time to time.

Section 1.23 **"Foreign Currency"** shall mean any currency other than Dollars.

Section 1.24 **"Full Entitlement ADR(s)", "Full Entitlement ADS(s)" and "Full Entitlement Share(s)"** shall have the respective meanings set forth in Section 2.12.

Section 1.25 **"Holder(s)"** shall mean the person(s) in whose name the ADSs are registered on the books of the Depositary (or the Registrar, if any) maintained for such purpose. A Holder may or may not be a Beneficial Owner. If a Holder is not the Beneficial Owner of the ADS(s) registered in its name, such person shall be deemed, for all purposes hereunder, to have all requisite authority to act on behalf of the Beneficial Owners of the ADSs registered in its name. The manner in which a Holder holds ADSs (e.g., in certificated vs. uncertificated form) may affect the rights and obligations of, and the manner in which, and the extent to which, the services are made available to, Holders pursuant to the terms of the Deposit Agreement.

Section 1.26 **"Partial Entitlement ADR(s)", "Partial Entitlement ADS(s)" and "Partial Entitlement Share(s)"** shall have the respective meanings set forth in Section 2.12.

Section 1.27 **"Pounds", "Pence" and "£"** shall refer to the lawful currency of England.

Section 1.28 **"Principal Office"** shall mean, when used with respect to the Depositary, the principal office of the Depositary at which at any particular time its depositary receipts business shall be administered, which, at the date of the Deposit Agreement, is located at 388 Greenwich Street, New York, New York 10013, U.S.A.

Section 1.29 **"Registrar"** shall mean the Depositary or any bank or trust company having an office in the Borough of Manhattan, The City of New York, which shall be appointed by the Depositary to register issuances, transfers and cancellations of ADSs as herein provided, and shall include any co-registrar appointed by the Depositary for such purposes. Registrars (other than the Depositary) may be removed and substitutes appointed by the Depositary. Each Registrar (other than the Depositary) appointed pursuant to the Deposit Agreement shall be required to give notice in writing to the Depositary accepting such appointment and agreeing to be bound by the applicable terms of the Deposit Agreement.

Section 1.30 **"Restricted Securities"** shall mean Shares, Deposited Securities or ADSs which (i) have been acquired directly or indirectly from the Company or any of its Affiliates in a transaction or chain of transactions not involving any public offering and are subject to resale limitations under the Securities Act or the rules issued thereunder, or (ii) are held by an executive officer or director (or persons performing similar functions) or other Affiliate of the Company, or (iii) are subject to other restrictions on sale or deposit under the laws of the United States, England and Wales, or under a shareholder agreement or the Articles of Association of the Company or under the regulations of an applicable securities exchange unless, in each case, such Shares, Deposited Securities or ADSs are being transferred or sold to persons other than an Affiliate of the Company in a transaction (a) covered by an effective resale registration statement, or (b) exempt from the registration requirements of the Securities Act (as hereinafter defined), and the Shares, Deposited Securities or ADSs are not, when held by such person(s), Restricted Securities.

Section 1.31 **"Restricted ADR(s)", "Restricted ADS(s)" and "Restricted Shares"** shall have the respective meanings set forth in Section 2.14.

Section 1.32 **"Securities Act"** shall mean the United States Securities Act of 1933, as amended from time to time.

Section 1.33 **"Share Registrar"** shall mean Computershare Investor Services plc, a company registered in England and Wales or any other institution organized under the laws of England and Wales appointed by the Company to carry out the duties of registrar for the Shares, and any successor thereto.

Section 1.34 **"Shares"** shall mean the Company's ordinary shares, with a nominal value of £0.10 per share, validly issued and outstanding and fully paid and may, if the Depositary so agrees after consultation with the Company, include evidence of the right to receive Shares; provided that in no event shall Shares include evidence of the right to receive Shares with respect to which the full purchase price has not been paid or Shares as to which preemptive rights have theretofore not been validly waived or exercised; provided further, however, that, if there shall occur any change in nominal value, split-up, consolidation, reclassification, exchange, conversion or any other event described in Section 4.11 in respect of the Shares of the Company, the term "Shares" shall thereafter, to the maximum extent permitted by law, represent the successor securities resulting from such event.

Section 1.35 **"Uncertificated ADS(s)"** shall have the meaning set forth in Section 2.13.

Section 1.36 **"United States" and "U.S."** shall have the meaning assigned to it in Regulation S as promulgated by the Commission under the Securities Act.

ARTICLE II

APPOINTMENT OF DEPOSITARY; FORM OF RECEIPTS; DEPOSIT OF SHARES; EXECUTION AND DELIVERY, TRANSFER AND SURRENDER OF RECEIPTS

Section 2.1 **Appointment of Depositary.** The Company hereby appoints the Depositary as depositary for the Deposited Property and hereby authorizes and directs the Depositary to act in accordance with the terms and conditions set forth in the Deposit Agreement and the applicable ADRs. Each Holder and each Beneficial Owner, upon acceptance of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement shall be deemed for all purposes to (a) be a party to and bound by the terms of the Deposit Agreement and the applicable ADR(s), and (b) appoint the Depositary its attorney-in-fact, with full power to delegate, to act on its behalf and to take any and all actions contemplated in the Deposit Agreement and the applicable ADR(s), to adopt any and all procedures necessary to comply with applicable law and to take such action as the Depositary in its sole discretion may deem necessary or appropriate to carry out the purposes of the Deposit Agreement and the applicable ADR(s), the taking of such actions to be the conclusive determinant of the necessity and appropriateness thereof.

Section 2.2 **Form and Transferability of ADSs.**

(a) **Form.** Certificated ADSs shall be evidenced by definitive ADRs which shall be engraved, printed, lithographed or produced in such other manner as may be agreed upon by the Company and the Depositary. ADRs may be issued under the Deposit Agreement in denominations of any whole number of ADSs. The ADRs shall be substantially in the form set forth in Exhibit A to the Deposit Agreement, with any appropriate insertions, modifications and omissions, in each case as otherwise contemplated in the Deposit Agreement or required by law. ADRs shall be (i) dated, (ii) signed by the manual or facsimile signature of a duly authorized signatory of the Depositary, (iii) countersigned by the manual or facsimile signature of a duly authorized signatory of the Registrar, and (iv) registered in the books maintained by the Registrar for the registration of issuances and transfers of ADSs. No ADR and no Certificated ADS evidenced thereby shall be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company, unless such ADR shall have been so dated, signed, countersigned and registered. ADRs bearing the facsimile signature of a duly-authorized signatory of the Depositary or the Registrar, who at the time of signature was a duly-authorized signatory of the Depositary or the Registrar, as the case may be, shall bind the Depositary, notwithstanding the fact that such signatory has ceased to be so authorized prior to the Delivery of such ADR by the Depositary. The ADRs shall bear a CUSIP number that is different from any CUSIP number that was, is or may be assigned to any depositary receipts previously or subsequently issued pursuant to any other arrangement between the Depositary (or any other depositary) and the Company and which are not ADRs outstanding hereunder.

(b) **Legends.** The ADRs may be endorsed with, or have incorporated in the text thereof, such legends or recitals not inconsistent with the provisions of the Deposit Agreement as may be (i) necessary to enable the Depositary and the Company to perform their respective obligations hereunder, (ii) required to comply with any applicable laws or regulations, or with the rules and regulations of any securities exchange or market upon which ADSs may be traded, listed or quoted, or to conform with any usage with respect thereto, (iii) necessary to indicate any special limitations or restrictions to which any particular ADRs or ADSs are subject by reason of the date of issuance of the Deposited Securities or otherwise, or (iv) required by any book-entry system in which the ADSs are held. Holders and Beneficial Owners shall be deemed, for all purposes, to have notice of, and to be bound by, the terms and conditions of the legends set forth, in the case of Holders, on the ADR registered in the name of the applicable Holders or, in the case of Beneficial Owners, on the ADR representing the ADSs owned by such Beneficial Owners.

(c) **Title.** Subject to the limitations contained herein and in the ADR, title to an ADR (and to each Certificated ADS evidenced thereby) shall be transferable upon the same terms as a certificated security under the laws of the State of New York, provided that, in the case of Certificated ADSs, such ADR has been properly endorsed or is accompanied by proper instruments of transfer. Notwithstanding any notice to the contrary, the Depositary and the Company may deem and treat the Holder of an ADS (that is, the person in whose name an ADS is registered on the books of the Depositary) as the absolute owner thereof for all purposes. Neither the Depositary nor the Company shall have any obligation nor be subject to any liability under the Deposit Agreement or any ADR to any holder or any Beneficial Owner unless, in the case of a holder of ADSs, such holder is the Holder registered on the books of the Depositary or, in the case of a Beneficial Owner, such Beneficial Owner, or the Beneficial Owner's representative, is the Holder registered on the books of the Depositary.

(d) **Book-Entry Systems.** The Depositary shall make arrangements for the acceptance of the ADSs into DTC. All ADSs held through DTC will be registered in the name of the nominee for DTC (currently "Cede & Co."). The nominee of DTC will be the only "Holder" of all ADSs held through DTC. Unless issued by the Depositary as Uncertificated ADSs, the ADSs registered in the name of Cede & Co. will be evidenced by one or more ADR(s) in the form of a "Balance Certificate," which will provide that it represents the aggregate number of ADSs from time to time indicated in the records of the Depositary as being issued hereunder and that the aggregate number of ADSs represented thereby may from time to time be increased or decreased by making adjustments on such records of the Depositary and of DTC or its nominee as hereinafter provided. Citibank, N.A. (or such other entity as is appointed by DTC or its nominee) may hold the "Balance Certificate" as custodian for DTC. Each Beneficial Owner of ADSs held through DTC must rely upon the procedures of DTC and the DTC Participants to exercise or be entitled to any rights attributable to such ADSs. The DTC Participants shall for all purposes be deemed to have all requisite power and authority to act on behalf of the Beneficial Owners of the ADSs held in the DTC Participants' respective accounts in DTC and the Depositary shall for all purposes be authorized to rely upon any instructions and information given to it by DTC Participants. So long as ADSs are held through DTC or unless otherwise required by law, ownership of beneficial interests in the ADSs registered in the name of the nominee for DTC will be shown on, and transfers of such ownership will be effected only through, records maintained by (i) DTC or its nominee (with respect to the interests of DTC Participants), or (ii) DTC Participants or their nominees (with respect to the interests of clients of DTC Participants). Any distributions made, and any notices given, by the Depositary to DTC under the terms of the Deposit Agreement shall (unless otherwise specified by the Depositary) satisfy the Depositary's obligations under the Deposit Agreement to make such distributions, and give such notices, in respect of the ADSs held in DTC (including, for avoidance of doubt, to the DTC Participants holding the ADSs in their DTC accounts and to the Beneficial Owners of such ADSs).

Section 2.3 **Deposit of Shares.** Subject to the terms and conditions of the Deposit Agreement and applicable law, Shares or evidence of rights to receive Shares (other than Restricted Securities) may be deposited by any person (including the Depositary in its individual capacity but subject, however, in the case of the Company or any Affiliate of the Company, to Section 5.7) at any time, whether or not the transfer books of the Company or the Share Registrar, if any, are closed, by Delivery of the Shares to the Custodian. Every deposit of Shares shall be accompanied by the following: (A) (i) *in the case of Shares represented by certificates issued in registered form*, the certificate(s) representing such Shares and, where relevant, appropriate instruments of transfer or endorsement, in a form reasonably satisfactory to the Custodian, (ii) *in the case of Shares represented by certificates in bearer form*, the requisite coupons and talons pertaining thereto, and (iii) *in the case of Shares delivered by book-entry transfer and recordation*, confirmation of such book-entry transfer and recordation in the books of the Share Registrar or of CREST, as applicable, to the Custodian or that irrevocable instructions have been given to cause such Shares to be so issued or transferred, as applicable, and recorded, (B) such certifications and payments (including, without limitation, the Depositary's fees and related charges) and evidence of such payments (including, without limitation, stamping or otherwise marking such Shares by way of receipt) as may be reasonably required by the Depositary or the Custodian in accordance with the provisions of the Deposit Agreement and applicable law, (C) if the Depositary so requires, a written order directing the Depositary to issue and deliver to, or upon the written order of, the person(s) stated in such order the number of ADSs representing the Shares so deposited, (D) evidence reasonably satisfactory to the Depositary (which may be an opinion of counsel) that all necessary approvals have been granted by, or there has been compliance with the rules and regulations of, any applicable governmental agency in England and Wales, and (E) if the Depositary so requires, (i) an agreement, assignment or instrument reasonably satisfactory to the Depositary or the Custodian which provides for the prompt transfer by any person in whose name the Shares are or have been recorded to the Custodian of any distribution, or right to subscribe for additional Shares or to receive other property in respect of any such deposited Shares or, in lieu thereof, such indemnity or other agreement as shall be reasonably satisfactory to the Depositary or the Custodian and (ii) if the Shares are registered in the name of the person on whose behalf they are presented for deposit, a proxy or proxies entitling the Custodian to exercise voting rights in respect of the Shares for any and all purposes until the Shares so deposited are registered in the name of the Depositary, the Custodian or any nominee.

Without limiting any other provision of the Deposit Agreement, the Depositary shall instruct the Custodian not to, and the Depositary shall not knowingly, accept for deposit (a) any Restricted Securities (except as contemplated by Section 2.14) nor (b) any fractional Shares or fractional Deposited Securities nor (c) a number of Shares or Deposited Securities which upon application of the ADS to Shares ratio would give rise to fractional ADSs. No Shares shall be accepted for deposit unless accompanied by evidence, if any is required by the Depositary, that is reasonably satisfactory to the Depositary or the Custodian that all conditions to such deposit have been satisfied by the person depositing such Shares under the laws and regulations of England and Wales and any necessary approval has been granted by any applicable governmental body in England and Wales, if any. The Depositary may issue ADSs against evidence of rights to receive Shares from the Company, any agent of the Company or any custodian, registrar, transfer agent, clearing agency or other entity involved in ownership or transaction records in respect of the Shares. Such evidence of rights shall consist of written blanket or specific guarantees of ownership of Shares furnished by the Company or any such custodian, registrar, transfer agent, clearing agency or other entity involved in ownership or transaction records in respect of the Shares.

Without limitation of the foregoing, the Depositary shall not knowingly accept for deposit under the Deposit Agreement (A) any Shares or other securities required to be registered under the provisions of the Securities Act, unless (i) a registration statement is in effect as to such Shares or other securities or (ii) the deposit is made upon terms contemplated in Section 2.14, or (B) any Shares or other securities the deposit of which would violate any provisions of the Articles of Association of the Company or English law. For purposes of the foregoing sentence, the Depositary shall be entitled to rely upon representations and warranties made or deemed made pursuant to the Deposit Agreement and shall not be required to make any further investigation. The Depositary will comply with written instructions of the Company (received by the Depositary reasonably in advance) not to accept for deposit hereunder any Shares identified in such instructions at such times and under such circumstances as may reasonably be specified in such instructions in order to facilitate the Company's compliance with the securities laws of the United States.

Section 2.4 **Registration and Safekeeping of Deposited Securities**. The Depositary shall instruct the Custodian upon each Delivery of registered Shares being deposited hereunder with the Custodian (or other Deposited Securities pursuant to Article IV hereof), together with the other documents above specified, to present such Shares, together with the appropriate instrument(s) of transfer or endorsement, duly stamped, to the Share Registrar for transfer and registration of the Shares (as soon as transfer and registration can be accomplished and at the expense of the person for whom the deposit is made) in the name of the Depositary, the Custodian or a nominee of either. Deposited Securities shall be held by the Depositary, or by a Custodian for the account and to the order of the Depositary or a nominee of the Depositary, in each case, on behalf of the Holders and Beneficial Owners, at such place(s) as the Depositary or the Custodian shall determine. Notwithstanding anything else contained in the Deposit Agreement, any ADR(s), or any other instruments or agreements relating to the ADSs and the corresponding Deposited Property, the registration of the Deposited Securities in the name of the Depositary, the Custodian or any of their respective nominees, shall, to the maximum extent permitted by applicable law, vest in the Depositary, the Custodian or the applicable nominee the record ownership in the applicable Deposited Securities with the beneficial ownership rights and interests in such Deposited Securities being at all times vested with the Beneficial Owners of the ADSs representing the Deposited Securities. Notwithstanding the foregoing, the Depositary, the Custodian and the applicable nominee shall at all times be entitled to exercise the beneficial ownership rights in all Deposited Property, in each case only on behalf of the Holders and Beneficial Owners of the ADSs representing the Deposited Property, upon the terms set forth in the Deposit Agreement and, if applicable, the ADR(s) representing the ADSs. The Depositary, the Custodian and their respective nominees shall for all purposes be deemed to have all requisite power and authority to act in respect of Deposited Property on behalf of the Holders and Beneficial Owners of ADSs representing the Deposited Property, and upon making payments to, or acting upon instructions from, or information provided by, the Depositary, the Custodian or their respective nominees all persons shall be authorized to rely upon such power and authority

Section 2.5 **Issuance of ADSs.** The Depositary has made arrangements with the Custodian for the Custodian to confirm to the Depositary upon receipt of a deposit of Shares (i) that a deposit of Shares has been made pursuant to Section 2.3, (ii) that such Deposited Securities have been recorded in the name of the Depositary, the Custodian or a nominee of either on the shareholders' register maintained by or on behalf of the Company by the Share Registrar on the books of CREST, (iii) that all required documents have been received, and (iv) the person(s) to whom or upon whose order ADSs are deliverable in respect thereof and the number of ADSs to be so delivered. Such notification may be made by letter, cable, telex, SWIFT message or, at the risk and expense of the person making the deposit, by facsimile or other means of electronic transmission. Upon receiving such notice from the Custodian, the Depositary, subject to the terms and conditions of the Deposit Agreement and applicable law, shall issue the ADSs representing the Shares so deposited to or upon the order of the person(s) named in the notice delivered to the Depositary and, if applicable, shall execute and deliver at its Principal Office Receipt(s) registered in the name(s) requested by such person(s) and evidencing the aggregate number of ADSs to which such person(s) are entitled, but, in each case, only upon payment to the Depositary of the charges of the Depositary for accepting a deposit of Shares and issuing ADSs (as set forth in Section 5.9 and Exhibit B hereto) and all taxes and governmental charges and fees payable in connection with such deposit and the transfer of the Shares and the issuance of the ADS(s). The Depositary shall only issue ADSs in whole numbers and deliver, if applicable, ADR(s) evidencing whole numbers of ADSs.

Section 2.6 **Transfer, Combination and Split-up of ADRs.**

(a) **Transfer.** The Registrar shall register the transfer of ADRs (and of the ADSs represented thereby) on the books maintained for such purpose and the Depositary shall (x) cancel such ADRs and execute new ADRs evidencing the same aggregate number of ADSs as those evidenced by the ADRs canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs and (z) Deliver such new ADRs to or upon the order of the person entitled thereto, if each of the following conditions has been satisfied: (i) the ADRs have been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a transfer thereof, (ii) the surrendered ADRs have been properly endorsed or are accompanied by proper instruments of transfer (including signature guarantees in accordance with standard securities industry practice), (iii) the surrendered ADRs have been duly stamped (if required by the laws of the State of New York or of the United States), and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B hereto) have been paid, *subject, however, in each case,* to the terms and conditions of the applicable ADRs, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

(b) **Combination & Split-Up.** The Registrar shall register the split-up or combination of ADRs (and of the ADSs represented thereby) on the books maintained for such purpose and the Depositary shall (x) cancel such ADRs and execute new ADRs for the number of ADSs requested, but in the aggregate not exceeding the number of ADSs evidenced by the ADRs canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs and (z) Deliver such new ADRs to or upon the order of the Holder thereof, if each of the following conditions has been satisfied: (i) the ADRs have been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a split-up or combination thereof, and (ii) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B hereto) have been paid, *subject, however, in each case*, to the terms and conditions of the applicable ADRs, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

Section 2.7 **Surrender of ADSs and Withdrawal of Deposited Securities**. The Holder of ADSs shall be entitled to Delivery (at the Custodian's designated office) of the Deposited Securities at the time represented by the ADSs upon satisfaction of each of the following conditions: (i) the Holder (or a duly-authorized attorney of the Holder) has duly Delivered ADSs to the Depositary at its Principal Office (and if applicable, the ADRs evidencing such ADSs) for the purpose of withdrawal of the Deposited Securities represented thereby, (ii) if applicable and so required by the Depositary, the ADRs Delivered to the Depositary for such purpose have been properly endorsed in blank or are accompanied by proper instruments of transfer in blank (including signature guarantees in accordance with standard securities industry practice), (iii) if so required by the Depositary, the Holder of the ADSs has executed and delivered to the Depositary a written order directing the Depositary to cause the Deposited Securities being withdrawn to be Delivered to or upon the written order of the person(s) designated in such order, and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 and Exhibit B) have been paid, *subject, however, in each case*, to the terms and conditions of the ADRs evidencing the surrendered ADSs, of the Deposit Agreement, of the Company's Articles of Association and of any applicable laws and the rules of CREST, and to any provisions of or governing the Deposited Securities , in each case as in effect at the time thereof.

Upon satisfaction of each of the conditions specified above, the Depositary (i) shall cancel the ADSs Delivered to it (and, if applicable, the ADR(s) evidencing the ADSs so Delivered), (ii) shall direct the Registrar to record the cancellation of the ADSs so Delivered on the books maintained for such purpose, and (iii) shall direct the Custodian to Deliver, or cause the Delivery of, in each case, without unreasonable delay, the Deposited Securities represented by the ADSs so canceled together with any certificate or other document of title for the Deposited Securities, or evidence of the electronic transfer thereof (if available), as the case may be, to or upon the written order of the person(s) designated in the order delivered to the Depositary for such purpose, *subject however, in each case*, to the terms and conditions of the Deposit Agreement, of the ADRs evidencing the ADSs so canceled, of the Articles of Association of the Company, of any applicable laws and of the rules of CREST, and to the terms and conditions of or governing the Deposited Securities, in each case as in effect at the time thereof.

The Depositary shall not accept for surrender ADSs representing less than one (1) Share. In the case of Delivery to it of ADSs representing a number other than a whole number of Shares, the Depositary shall cause ownership of the appropriate whole number of Shares to be Delivered in accordance with the terms hereof, and shall, at the discretion of the Depositary, either (i) return to the person surrendering such ADSs the number of ADSs representing any remaining fractional Share, or (ii) sell or cause to be sold the fractional Share represented by the ADSs so surrendered and remit the proceeds of such sale (net of (a) applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld as a result of such sale) to the person surrendering the ADSs.

Notwithstanding anything else contained in any ADR or the Deposit Agreement, the Depositary may make delivery at the Principal Office of the Depositary of Deposited Property consisting of (i) any cash dividends or cash distributions, or (ii) any proceeds from the sale of any non-cash distributions, which are at the time held by the Depositary in respect of the Deposited Securities represented by the ADSs surrendered for cancellation and withdrawal. At the request, risk and expense of any Holder so surrendering ADSs, and for the account of such Holder, the Depositary shall direct the Custodian to forward (to the extent permitted by law) any Deposited Property (other than Deposited Securities) held by the Custodian in respect of such ADSs to the Depositary for delivery at the Principal Office of the Depositary. Such direction shall be given by letter or, at the request, risk and expense of such Holder, by cable, telex or facsimile transmission.

Section 2.8 Limitations on Execution and Delivery, Transfer, etc. of ADSs; Suspension of Delivery, Transfer, etc.

(a) **Additional Requirements.** As a condition precedent to the execution and Delivery, the registration of issuance, transfer, split-up, combination or surrender, of any ADS, the delivery of any distribution thereon, or the withdrawal of any Deposited Property, the Depositary or the Custodian may require (i) payment from the depositor of Shares or presenter of ADSs or of an ADR of a sum sufficient to reimburse it for any tax or other governmental charge and any stock transfer or registration fee with respect thereto (including any such tax or charge and fee with respect to Shares being deposited or withdrawn) and payment of any applicable fees and charges of the Depositary as provided in Section 5.9 and Exhibit B, (ii) the production of proof reasonably satisfactory to it as to the identity and genuineness of any signature or any other matter contemplated by Section 3.1, and (iii) compliance with (A) any laws or governmental regulations relating to the execution and Delivery of ADRs or ADSs or to the withdrawal of Deposited Securities and (B) such reasonable regulations as the Depositary and the Company may establish consistent with the provisions of the representative ADR, if applicable, the Deposit Agreement and applicable law.

(b) **Additional Limitations.** The issuance of ADSs against deposits of Shares generally or against deposits of particular Shares may be suspended, or the deposit of particular Shares may be refused, or the registration of transfer of ADSs in particular instances may be refused, or the registration of transfers of ADSs generally may be suspended, during any period when the transfer books of the Company, the Depositary, a Registrar or the Share Registrar are closed or if any such action is deemed necessary or advisable by the Depositary or the Company, in good faith, at any time or from time to time because of any requirement of law or regulation, any government or governmental body or commission or any securities exchange on which the ADSs or Shares are listed, or under any provision of the Deposit Agreement or the representative ADR(s), if applicable, or under any provision of, or governing, the Deposited Securities, or because of a meeting of shareholders of the Company or for any other reason, subject, in all cases, to Section 7.8(a).

(c) **Regulatory Restrictions.** Notwithstanding any provision of the Deposit Agreement or any ADR(s) to the contrary, Holders are entitled to surrender outstanding ADSs to withdraw the Deposited Securities associated herewith at any time subject only to (i) temporary delays caused by closing the transfer books of the Depositary or the Company or the deposit of Shares in connection with voting at a shareholders' meeting or the payment of dividends, (ii) the payment of fees, taxes and similar charges, (iii) compliance with any U.S. or foreign laws or governmental regulations relating to the ADSs or to the withdrawal of the Deposited Securities, and (iv) other circumstances specifically contemplated by Instruction I.A.(l) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time).

Section 2.9 Lost ADRs, etc. In case any ADR shall be mutilated, destroyed, lost, or stolen, the Depositary shall execute and deliver a new ADR of like tenor at the expense of the Holder (a) *in the case of a mutilated ADR,* in exchange of and substitution for such mutilated ADR upon cancellation thereof, or (b) *in the case of a destroyed, lost or stolen ADR,* in lieu of and in substitution for such destroyed, lost, or stolen ADR, after the Holder thereof (i) has submitted to the Depositary a written request for such exchange and substitution before the Depositary has notice that the ADR has been acquired by a bona fide purchaser, (ii) has provided such security or indemnity (including an indemnity bond) as may be required by the Depositary to save it and any of its agents harmless, and (iii) has satisfied any other reasonable requirements imposed by the Depositary, including, without limitation, evidence satisfactory to the Depositary of such destruction, loss or theft of such ADR, the authenticity thereof and the Holder's ownership thereof.

Section 2.10 Cancellation and Destruction of Surrendered ADRs; Maintenance of Records. All ADRs surrendered to the Depositary shall be canceled by the Depositary. Canceled ADRs shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable against the Depositary for any purpose. The Depositary is authorized to destroy ADRs so canceled, provided the Depositary maintains a record of all destroyed ADRs. Any ADSs held in book-entry form (*e.g.*, through accounts at DTC) shall be deemed canceled when the Depositary causes the number of ADSs evidenced by the Balance Certificate to be reduced by the number of ADSs surrendered (without the need to physically destroy the Balance Certificate).

Section 2.11 Escheatment. In the event any unclaimed property relating to the ADSs, for any reason, is in the possession of Depositary and has not been claimed by the Holder thereof or cannot be delivered to the Holder thereof through usual channels, the Depositary shall, upon expiration of any applicable statutory period relating to abandoned property laws, escheat such unclaimed property to the relevant authorities in accordance with the laws of each of the relevant States of the United States.

Section 2.12 **Partial Entitlement ADSs.** In the event any Shares are deposited which (i) entitle the holders thereof to receive a per-share distribution or other entitlement in an amount different from the Shares then on deposit or (ii) are not fully fungible (including, without limitation, as to settlement or trading) with the Shares then on deposit (the Shares then on deposit collectively, "Full Entitlement Shares" and the Shares with different entitlement, "Partial Entitlement Shares"), the Depositary shall (i) cause the Custodian to hold Partial Entitlement Shares separate and distinct from Full Entitlement Shares, and (ii) subject to the terms of the Deposit Agreement, issue ADSs representing Partial Entitlement Shares which are separate and distinct from the ADSs representing Full Entitlement Shares, by means of separate CUSIP numbering and legending (if necessary) and, if applicable, by issuing ADRs evidencing such ADSs with applicable notations thereon ("Partial Entitlement ADSs/ADRs" and "Full Entitlement ADSs/ADRs", respectively). If and when Partial Entitlement Shares become Full Entitlement Shares, the Depositary shall (a) give notice thereof to Holders of Partial Entitlement ADSs and give Holders of Partial Entitlement ADRs the opportunity to exchange such Partial Entitlement ADRs for Full Entitlement ADRs, (b) cause the Custodian to transfer the Partial Entitlement Shares into the account of the Full Entitlement Shares, and (c) take such actions as are necessary to remove the distinctions between (i) the Partial Entitlement ADRs and ADSs, on the one hand, and (ii) the Full Entitlement ADRs and ADSs on the other. Holders and Beneficial Owners of Partial Entitlement ADSs shall only be entitled to the entitlements of Partial Entitlement Shares. Holders and Beneficial Owners of Full Entitlement ADSs shall be entitled only to the entitlements of Full Entitlement Shares. All provisions and conditions of the Deposit Agreement shall apply to Partial Entitlement ADRs and ADSs to the same extent as Full Entitlement ADRs and ADSs, except as contemplated by this Section 2.12. The Depositary is authorized to take any and all other actions as may be necessary (including, without limitation, making the necessary notations on ADRs) to give effect to the terms of this Section 2.12. The Company agrees to give timely written notice to the Depositary if any Shares issued or to be issued are Partial Entitlement Shares and shall assist the Depositary with the establishment of procedures enabling the identification of Partial Entitlement Shares upon Delivery to the Custodian.

Section 2.13 **Certificated/Uncertificated ADSs.** Notwithstanding any other provision of the Deposit Agreement, the Depositary may, at any time and from time to time, issue ADSs that are not evidenced by ADRs (such ADSs, the "Uncertificated ADS(s)" and the ADS(s) evidenced by ADR(s), the "Certificated ADS(s)"). When issuing and maintaining Uncertificated ADS(s) under the Deposit Agreement, the Depositary shall at all times be subject to (i) the standards applicable to registrars and transfer agents maintaining direct registration systems for equity securities in New York and issuing uncertificated securities under New York law, and (ii) the terms of New York law applicable to uncertificated equity securities. Uncertificated ADSs shall not be represented by any instruments but shall be evidenced by registration in the books of the Depositary maintained for such purpose. Holders of Uncertificated ADSs, that are not subject to any registered pledges, liens, restrictions or adverse claims of which the Depositary has notice at such time, shall at all times have the right to exchange the Uncertificated ADS(s) for Certificated ADS(s) of the same type and class, subject in each case to (x) the applicable laws and any rules and regulations the Depositary may have established in respect of the Uncertificated ADSs, and (y) the continued availability of Certificated ADSs in the U.S. Holders of Certificated ADSs shall, if the Depositary maintains a direct registration system for the ADSs, have the right to exchange the Certificated ADSs for Uncertificated ADSs upon (i) the due surrender of the Certificated ADS(s)

to the Depositary for such purpose and (ii) the presentation of a written request to that effect to the Depositary, subject in each case to (a) all liens and restrictions noted on the ADR evidencing the Certificated ADS(s) and all adverse claims of which the Depositary then has notice, (b) the terms of the Deposit Agreement and the rules and regulations that the Depositary may establish for such purposes hereunder, (c) applicable law, and (d) payment of the Depositary fees and expenses applicable to such exchange of Certificated ADS(s) for Uncertificated ADS(s). Uncertificated ADSs shall in all material respects be identical to Certificated ADS(s) of the same type and class, except that (i) no ADR(s) shall be, or shall need to be, issued to evidence Uncertificated ADS(s), (ii) Uncertificated ADS(s) shall, subject to the terms of the Deposit Agreement, be transferable upon the same terms and conditions as uncertificated securities under New York law, (iii) the ownership of Uncertificated ADS(s) shall be recorded on the books of the Depositary maintained for such purpose and evidence of such ownership shall be reflected in periodic statements provided by the Depositary to the Holder(s) in accordance with applicable New York law, (iv) the Depositary may from time to time, upon notice to the Holders of Uncertificated ADSs affected thereby, establish rules and regulations, and amend or supplement existing rules and regulations, as may be deemed reasonably necessary to maintain Uncertificated ADS(s) on behalf of Holders, provided that (a) such rules and regulations do not conflict with the terms of the Deposit Agreement and applicable law, and (b) the terms of such rules and regulations are readily available to Holders upon request, (v) the Uncertificated ADS(s) shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company unless such Uncertificated ADS(s) is/are registered on the books of the Depositary maintained for such purpose, (vi) the Depositary may, in connection with any deposit of Shares resulting in the issuance of Uncertificated ADSs and with any transfer, pledge, release and cancellation of Uncertificated ADSs, require the prior receipt of such documentation as the Depositary may deem reasonably appropriate, and (vii) upon termination of the Deposit Agreement, the Depositary shall not require Holders of Uncertificated ADSs to affirmatively instruct the Depositary before remitting proceeds from the sale of the Deposited Property represented by such Holders' Uncertificated ADSs under the terms of Section 6.2 of the Deposit Agreement. When issuing ADSs under the terms of the Deposit Agreement, including, without limitation, issuances pursuant to Sections 2.5, 4.2, 4.3, 4.4, 4.5 and 4.11, the Depositary may in its discretion determine to issue Uncertificated ADSs rather than Certificated ADSs, unless otherwise specifically instructed by the applicable Holder to issue Certificated ADSs. All provisions and conditions of the Deposit Agreement shall apply to Uncertificated ADSs to the same extent as to Certificated ADSs, except as contemplated by this Section 2.13. The Depositary is authorized and directed to take any and all actions and establish any and all procedures deemed reasonably necessary to give effect to the terms of this Section 2.13. Any references in the Deposit Agreement or any ADR(s) to the terms “American Depositary Share(s)” or “ADS(s)” shall, unless the context otherwise requires, include Certificated ADS(s) and Uncertificated ADS(s). Except as set forth in this Section 2.13 and except as required by applicable law, the Uncertificated ADSs shall be treated as ADSs issued and outstanding under the terms of the Deposit Agreement. In the event that, in determining the rights and obligations of parties hereto with respect to any Uncertificated ADSs, any conflict arises between (a) the terms of the Deposit Agreement (other than this Section 2.13) and (b) the terms of this Section 2.13, the terms and conditions set forth in this Section 2.13 shall be controlling and shall govern the rights and obligations of the parties to the Deposit Agreement pertaining to the Uncertificated ADSs.

Section 2.14 **Restricted ADSs.** The Depositary shall, at the request and expense of the Company, establish procedures enabling the deposit hereunder of Shares that are Restricted Securities in order to enable the holder of such Shares to hold its ownership interests in such Restricted Securities in the form of ADSs issued under the terms hereof (such Shares, "Restricted Shares"). Upon receipt of a written request from the Company to accept Restricted Shares for deposit hereunder, the Depositary agrees to establish procedures permitting the deposit of such Restricted Shares and the issuance of ADSs representing the right to receive, subject to the terms of the Deposit Agreement and the applicable ADR (if issued as a Certificated ADS), such deposited Restricted Shares (such ADSs, the "Restricted ADSs," and the ADRs evidencing such Restricted ADSs, the "Restricted ADRs"). Notwithstanding anything contained in this Section 2.14, the Depositary and the Company may, to the extent not prohibited by law, agree to issue the Restricted ADSs in uncertificated form ("Uncertificated Restricted ADSs") upon such terms and conditions as the Company and the Depositary may deem necessary and appropriate. The Company shall assist the Depositary in the establishment of such procedures and agrees that it shall take all steps necessary and satisfactory to the Depositary to ensure that the establishment of such procedures does not violate the provisions of the Securities Act or any other applicable laws. The depositors of such Restricted Shares and the Holders of the Restricted ADSs may be required prior to the deposit of such Restricted Shares, the transfer of the Restricted ADRs and Restricted ADSs or the withdrawal of the Restricted Shares represented by Restricted ADSs to provide such written certifications or agreements as the Depositary or the Company may require. The Company shall provide to the Depositary in writing the legend(s) to be affixed to the Restricted ADRs (if the Restricted ADSs are to be issued as Certificated ADSs**)**, or to be included in the statements issued from time to time to Holders of Uncertificated ADSs (if issued as Uncertificated Restricted ADSs), which legends shall (i) be in a form reasonably satisfactory to the Depositary and (ii) contain the specific circumstances under which the Restricted ADSs, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, may be transferred or the Restricted Shares withdrawn. The Restricted ADSs issued upon the deposit of Restricted Shares shall be separately identified on the books of the Depositary and the Restricted Shares so deposited shall, to the extent required by law, be held separate and distinct from the other Deposited Securities held hereunder. The Restricted ADSs shall not be eligible for inclusion in any book-entry settlement system, including, without limitation, DTC, and shall not in any way be fungible with the ADSs issued under the terms hereof that are not Restricted ADSs. The Restricted ADSs, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, shall be transferable only by the Holder thereof upon delivery to the Depositary of (i) all documentation otherwise contemplated by the Deposit Agreement and (ii) an opinion of counsel satisfactory to the Depositary setting forth, *inter alia*, the conditions upon which the Restricted ADSs presented, and, if applicable, the Restricted ADRs evidencing the Restricted ADSs, are transferable by the Holder thereof under applicable securities laws and the transfer restrictions contained in the legend applicable to the Restricted ADSs presented for transfer. Except as set forth in this Section 2.14 and except as required by applicable law, the Restricted ADSs and the Restricted ADRs evidencing Restricted ADSs shall be treated as ADSs and ADRs issued and outstanding under the terms of the Deposit Agreement. In the event that, in determining the rights and obligations of parties hereto with respect to any Restricted ADSs, any conflict arises between (a) the terms of the Deposit Agreement (other than this Section 2.14) and (b) the terms of (i) this Section 2.14 or (ii) the applicable Restricted ADR, the terms and conditions set forth in this Section 2.14 and of the Restricted ADR shall be controlling and shall govern the rights and obligations of the parties to the Deposit Agreement pertaining to the deposited Restricted Shares, the Restricted ADSs and Restricted ADRs.

If the Restricted ADRs, the Restricted ADSs and the Restricted Shares cease to be Restricted Securities, the Depositary, upon receipt of (x) an opinion of counsel satisfactory to the Depositary setting forth, *inter alia*, that the Restricted ADRs, the Restricted ADSs and the Restricted Shares are not as of such time Restricted Securities, and (y) instructions from the Company to remove the restrictions applicable to the Restricted ADRs, the Restricted ADSs and the Restricted Shares, shall (i) eliminate the distinctions and separations that may have been established between the applicable Restricted Shares held on deposit under this Section 2.14 and the other Shares held on deposit under the terms of the Deposit Agreement that are not Restricted Shares, (ii) treat the newly unrestricted ADRs and ADSs on the same terms as, and fully fungible with, the other ADRs and ADSs issued and outstanding under the terms of the Deposit Agreement that are not Restricted ADRs or Restricted ADSs, and (iii) take all actions necessary to remove any distinctions, limitations and restrictions previously existing under this Section 2.14 between the applicable Restricted ADRs and Restricted ADSs, respectively, on the one hand, and the other ADRs and ADSs that are not Restricted ADRs or Restricted ADSs, respectively, on the other hand, including, without limitation, by making the newly-unrestricted ADSs eligible for inclusion in the applicable book-entry settlement systems.

ARTICLE III

CERTAIN OBLIGATIONS OF HOLDERS AND BENEFICIAL OWNERS OF ADSs

Section 3.1 **Proofs, Certificates and Other Information.** Any person presenting Shares for deposit, any Holder and any Beneficial Owner may be required, and every Holder and Beneficial Owner agrees, from time to time to provide to the Depositary and the Custodian such proof of citizenship or residence, taxpayer status, payment of all applicable taxes or other governmental charges, exchange control approval, legal or beneficial ownership of ADSs and Deposited Property, compliance with applicable laws, the terms of the Deposit Agreement or the ADR(s) evidencing the ADSs and the provisions of, or governing, the Deposited Property, to execute such certifications and to make such representations and warranties, and to provide such other information and documentation (or, in the case of Shares in registered form presented for deposit, such information relating to the registration on the books of the Company or of the Share Registrar) as the Depositary or the Custodian may deem necessary or proper or as the Company may reasonably require by written request to the Depositary consistent with its obligations under the Deposit Agreement and the applicable ADR(s). The Depositary and the Registrar, as applicable, may and at the reasonable request of the Company, shall, to the extent practicable and subject to applicable law, withhold the execution or delivery or registration of transfer of any ADR or ADS or the distribution or sale of any dividend or distribution of rights or of the proceeds thereof or, to the extent not limited by the terms of Section 7.8(a), the delivery of any Deposited Property until such proof or other information is filed or such certifications are executed, or such representations and warranties are made, or such other documentation or information provided, in each case to the Depositary's, the Registrar's and the Company's satisfaction. The Depositary shall provide the Company, in a timely manner, with copies or originals if necessary and appropriate of (i) any such proofs of citizenship or residence, taxpayer status, or exchange control approval or copies of written representations and warranties which it receives from Holders and Beneficial Owners, and (ii) any other information or documents which the Company may reasonably request and which the Depositary shall request and receive from any Holder or Beneficial Owner or any person presenting Shares for deposit or ADSs for cancellation, transfer or withdrawal. Nothing herein shall obligate the Depositary to (i) obtain any information for the Company if not provided by the Holders or Beneficial Owners, or (ii) verify or vouch for the accuracy of the information so provided by the Holders or Beneficial Owners.

Section 3.2 **Liability for Taxes and Other Charges.** Any tax or other governmental charge payable by the Custodian or by the Depositary with respect to any Deposited Property, ADSs or ADRs shall be payable by the Holders and Beneficial Owners to the Depositary. The Company, the Custodian and/or the Depositary may withhold or deduct from any distributions made in respect of Deposited Property, and may sell for the account of a Holder and/or Beneficial Owner any or all of the Deposited Property and apply such distributions and sale proceeds in payment of, any taxes (including applicable interest and penalties) or charges that are or may be payable by Holders or Beneficial Owners in respect of the ADSs, Deposited Property and ADRs, the Holder and the Beneficial Owner remaining liable for any deficiency. The Custodian may refuse the deposit of Shares and the Depositary may refuse to issue ADSs, to deliver ADRs, register the transfer of ADSs, register the split-up or combination of ADRs and (subject to Section 7.8(a)) the withdrawal of Deposited Property until payment in full of such tax, charge, penalty or interest is received. Every Holder and Beneficial Owner agrees to indemnify the Depositary, the Company, the Custodian, and any of their agents, officers, employees and Affiliates for, and to hold each of them harmless from, any claims with respect to taxes (including applicable interest and penalties thereon) arising from any tax benefit obtained for such Holder and/or Beneficial Owner. The obligations of Holders and Beneficial Owners under this Section 3.2 shall survive any transfer of ADSs, any cancellation of ADSs and withdrawal of Deposited Securities, and the termination of the Deposit Agreement.

Section 3.3 **Representations and Warranties on Deposit of Shares.** Each person depositing Shares under the Deposit Agreement shall be deemed thereby to represent and warrant that (i) such Shares and the certificates therefor are duly authorized, validly allotted and issued, fully paid, not subject to any call for the payment of further capital and legally obtained by such person, (ii) all preemptive (and similar) rights, if any, with respect to such Shares have been validly waived, disapplied or exercised, (iii) the person making such deposit is duly authorized so to do, (iv) the Shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, (v) the Shares presented for deposit are not, and the ADSs issuable upon such deposit will not be, Restricted Securities (except as contemplated in Section 2.14), (vi) the Shares presented for deposit have not been stripped of any rights or entitlements, and (vii) the deposit of the Shares does not violate any applicable provisions of English law. Such representations and warranties shall survive the deposit and withdrawal of Shares, the issuance and cancellation of ADSs in respect thereof and the transfer of such ADSs. If any such representations or warranties are false in any way, the Company and the Depositary shall be authorized, at the cost and expense of the person depositing Shares, to take any and all actions necessary to correct the consequences thereof.

Section 3.4 **Compliance with Information Requests.** Notwithstanding any other provision of the Deposit Agreement or any ADR(s), each Holder and Beneficial Owner agrees to comply with requests from the Company pursuant to applicable law, the rules and requirements of any stock exchange on which the Shares or ADSs are, or will be, registered, traded or listed or the Articles of Association of the Company, which are made to provide information, *inter alia*, as to the capacity in which such Holder or Beneficial Owner owns ADSs (and Shares as the case may be) and regarding the identity of any other person(s) interested in such ADSs and the nature of such interest and various other matters, whether or not they are Holders and/or Beneficial Owners at the time of such request. The Depositary agrees to use its reasonable efforts to forward, upon the request of the Company and at the Company's expense, any such request from the Company to the Holders and to forward to the Company, as promptly as practicable, any such responses to such requests received by the Depositary.

Section 3.5 **Ownership Restrictions.** Notwithstanding any other provision in the Deposit Agreement or any ADR, the Company may restrict transfers of the Shares where such transfer might result in ownership of Shares exceeding limits imposed by applicable law or the Articles of Association of the Company. The Company may also restrict, in such manner as it deems appropriate, transfers of the ADSs where such transfer may result in the total number of Shares represented by the ADSs owned by a single Holder or Beneficial Owner to exceed any such limits. The Company may, in its sole discretion but subject to applicable law, instruct the Depositary to take action with respect to the ownership interest of any Holder or Beneficial Owner in excess of the limits set forth in the preceding sentence, including, but not limited to, the imposition of restrictions on the transfer of ADSs, the removal or limitation of voting rights or mandatory sale or disposition on behalf of a Holder or Beneficial Owner of the Shares represented by the ADSs held by such Holder or Beneficial Owner in excess of such limitations, if and to the extent such disposition is permitted by applicable law and the Articles of Association of the Company. Nothing herein shall be interpreted as obligating the Depositary or the Company to ensure compliance with the ownership restrictions described in this Section 3.5.

Notwithstanding any provision of the Deposit Agreement or of the ADRs and without limiting the foregoing, by being a Holder of an ADR, each such Holder agrees to provide such information as the Company may request in a disclosure notice (a "Disclosure Notice") given pursuant to the U.K. Companies Act 2006 (as amended from time to time and including any statutory modification or re-enactment thereof, the "Companies Act") or the Articles of Association of the Company. By accepting or holding an ADR, each Holder acknowledges that it understands that failure to comply with a Disclosure Notice may result in the imposition of sanctions against the holder of the Shares in respect of which the non-complying person is or was, or appears to be or has been, interested as provided in the Companies Act and the Articles of Association which currently include, the withdrawal of the voting rights of such Shares and the imposition of restrictions on the rights to receive dividends on and to transfer such Shares.

The Company reserves the right to instruct Holders to deliver their ADSs for cancellation and withdrawal of the Deposited Securities so as to permit the Company to deal directly with the Holder thereof as a holder of Shares and Holders agree to comply with such instructions. The Depositary agrees to cooperate with the Company in its efforts to inform Holders of the Company's exercise of its rights under this paragraph and agrees to consult with, and provide reasonable assistance without risk, liability or expense on the part of the Depositary, to the Company on the manner or manners in which it may enforce such rights with respect to any Holder.

Section 3.6 **Reporting Obligations and Regulatory Approvals.** Applicable laws and regulations may require holders and beneficial owners of Shares, including the Holders and Beneficial Owners of ADSs, to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. Holders and Beneficial Owners of ADSs are solely responsible for determining and complying with such reporting requirements and obtaining such approvals. Each Holder and each Beneficial Owner hereby agrees to make such determination, file such reports, and obtain such approvals to the extent and in the form required by applicable laws and regulations as in effect from time to time. Neither the Depositary, the Custodian, the Company or any of their respective agents or affiliates shall be required to take any actions whatsoever on behalf of Holders or Beneficial Owners to determine or satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

ARTICLE IV

THE DEPOSITED SECURITIES

Section 4.1 **Cash Distributions.** Whenever the Company intends to make a distribution of a cash dividend or other cash distribution in respect of any Deposited Securities, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable for determining the holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt of such notice, the Depositary shall establish an ADS Record Date upon the terms described in Section 4.9. Upon receipt of confirmation of the receipt of (x) any cash dividend or other cash distribution on any Deposited Securities, or (y) proceeds from the sale of any Deposited Property held in respect of the ADSs under the terms hereof, the Depositary will (i) if at the time of receipt thereof any amounts received in a Foreign Currency can, in the judgment of the Depositary (pursuant to Section 4.8), be converted on a practicable basis into Dollars transferable to the United States, promptly convert or cause to be converted such cash dividend, distribution or proceeds into Dollars (on the terms described in Section 4.8), (ii) if applicable and unless previously established, establish the ADS Record Date upon the terms described in Section 4.9, and (iii) distribute promptly the amount thus received (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld in connection with the distribution) to the Holders entitled thereto as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date. The Depositary shall distribute only such amount, however, as can be distributed without attributing to any Holder a fraction of one cent, and any balance not so distributed shall be held by the Depositary (without liability for interest thereon) and shall be added to and become part of the next sum received by the Depositary for distribution to Holders of ADSs outstanding at the time of the next distribution. If the Company, the Custodian or the Depositary is required to withhold and does withhold from any cash dividend or other cash distribution in respect of any Deposited Securities, or from any cash proceeds from the sales of Deposited Property, an amount on account of taxes, duties or other governmental charges, the amount distributed to Holders on the ADSs shall be reduced accordingly. Such withheld amounts shall be forwarded by the Company, the Custodian or the Depositary to the relevant governmental authority. Evidence of payment thereof by the Company shall be forwarded by the Company to the Depositary upon request. The Depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable Holders and Beneficial Owners of ADSs until the distribution can be effected or the funds that the Depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.1, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.1, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.1 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.2 **Distribution in Shares.** Whenever the Company intends to make a distribution that consists of a dividend in, or free distribution of, Shares, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution, specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt of such notice from the Company, the Depositary shall establish the ADS Record Date upon the terms described in Section 4.9. Upon receipt of confirmation from the Custodian of the receipt of the Shares so distributed by the Company, the Depositary shall either (i) subject to Section 5.9, distribute to the Holders as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date, additional ADSs, which represent in the aggregate the number of Shares received as such dividend, or free distribution, subject to the other terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld), or (ii) if additional ADSs are not so distributed, take all actions necessary so that each ADS issued and outstanding after the ADS Record Date shall, to the extent permissible by law, thenceforth also represent rights and interests in the additional integral number of Shares distributed upon the Deposited Securities represented thereby (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes). In lieu of delivering fractional ADSs, the Depositary shall sell the number of Shares or ADSs, as the case may be, represented by the aggregate of such fractions and distribute the net proceeds upon the terms described in Section 4.1. In the event that the Depositary determines that any distribution in property (including Shares) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, or, if the Company in the fulfillment of its obligation under Section 5.7, has furnished an opinion of U.S. counsel determining that Shares must be registered under the Securities Act or other laws in order to be distributed to Holders (and no such registration statement has been declared effective), the Depositary may dispose of all or a portion of such property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable, and the Depositary shall distribute the net proceeds of any such sale (after deduction of (a) applicable taxes required to be withheld, and (b) fees and charges of, and expenses incurred by, the Depositary) to Holders entitled thereto upon the terms described in Section 4.1. The Depositary shall hold and/or distribute any unsold balance of such property in accordance with the provisions of the Deposit Agreement. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.2, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.2, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.2 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.3 **Elective Distributions in Cash or Shares.** Whenever the Company intends to make a distribution payable at the election of the holders of Deposited Securities in cash or in additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such elective distribution and whether or not it wishes such elective distribution to be made available to Holders of ADSs. Upon the timely receipt of a notice indicating that the Company wishes such elective distribution to be made available to Holders of ADSs, the Depositary shall consult with the Company to determine, and the Company shall assist the Depositary in its determination, whether it is lawful and reasonably practicable to make such elective distribution available to the Holders of ADSs. The Depositary shall make such elective distribution available to Holders only if (i) the Company shall have timely requested that the elective distribution be made available to Holders, (ii) the Depositary shall have determined that such distribution is reasonably practicable and (iii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7. If the above conditions are not satisfied or if the Company requests such elective distribution not to be made available to Holders of ADSs, the Depositary shall establish the ADS Record Date on the terms described in Section 4.9 and, to the extent permitted by law, distribute to the Holders, on the basis of the same determination as is made in England and Wales in respect of the Shares for which no election is made, either (X) cash upon the terms described in Section 4.1 or (Y) additional ADSs representing such additional Shares upon the terms described in Section 4.2. If the above conditions are satisfied, the Depositary shall establish an ADS Record Date on the terms described in Section 4.9 and establish procedures to enable Holders to elect the receipt of the proposed distribution in cash or in additional ADSs. The Company shall assist the Depositary in establishing such procedures to the extent necessary. If a Holder elects to receive the proposed distribution (X) in cash, the distribution shall be made upon the terms described in Section 4.1, or (Y) in ADSs, the distribution shall be made upon the terms described in Section 4.2. Nothing herein shall obligate the Depositary to make available to Holders a method to receive the elective distribution in Shares (rather than ADSs). There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive elective distributions on the same terms and conditions as the holders of Shares. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for in this Section 4.3, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.3, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.3 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.4 Distribution of Rights to Purchase Additional ADSs.

(a) **Distribution to ADS Holders.** Whenever the Company intends to distribute to the holders of the Deposited Securities rights to subscribe for additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution and whether or not it wishes such rights to be made available to Holders of ADSs. Upon the timely receipt of a notice indicating that the Company wishes such rights to be made available to Holders of ADSs, the Depositary shall consult with the Company to determine, and the Company shall assist the Depositary in its determination, whether it is lawful and reasonably practicable to make such rights available to the Holders. The Depositary shall make such rights available to Holders only if (i) the Company shall have timely requested that such rights be made available to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7, and (iii) the Depositary shall have determined that such distribution of rights is reasonably practicable. In the event any of the conditions set forth above are not satisfied or if the Company requests that the rights not be made available to Holders of ADSs, the Depositary shall proceed with the sale of the rights as contemplated in Section 4.4(b) below. In the event all conditions set forth above are satisfied, the Depositary shall establish the ADS Record Date (upon the terms described in Section 4.9) and establish procedures to (x) distribute rights to purchase additional ADSs (by means of warrants or otherwise), (y) enable the Holders to exercise such rights (upon payment of the subscription price and of the applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes), and (z) deliver ADSs upon the valid exercise of such rights. The Company shall assist the Depositary to the extent necessary in establishing such procedures. Nothing herein shall obligate the Depositary to make available to the Holders a method to exercise rights to subscribe for Shares (rather than ADSs).

(b) **Sale of Rights.** If (i) the Company does not timely request the Depositary to make the rights available to Holders or requests that the rights not be made available to Holders, (ii) the Depositary fails to receive satisfactory documentation within the terms of Section 5.7, or determines it is not reasonably practicable to make the rights available to Holders, or (iii) any rights made available are not exercised and appear to be about to lapse, the Depositary shall determine whether it is lawful and reasonably practicable to sell such rights, in a riskless principal capacity, at such place and upon such terms (including public or private sale) as it may deem practicable. The Company shall assist the Depositary to the extent necessary to determine such legality and practicability. The Depositary shall, upon such sale, convert and distribute proceeds of such sale (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) upon the terms set forth in Section 4.1.

(c) **Lapse of Rights.** If the Depositary is unable to make any rights available to Holders upon the terms described in Section 4.4(a) or to arrange for the sale of the rights upon the terms described in Section 4.4(b), the Depositary shall allow such rights to lapse.

The Depositary shall not be liable for (i) any failure to accurately determine whether it may be lawful or practicable to make such rights available to Holders in general or any Holders in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or exercise, or (iii) the content of any materials forwarded to the Holders on behalf of the Company in connection with the rights distribution.

Notwithstanding anything to the contrary in this Section 4.4, if registration (under the Securities Act or any other applicable law) of the rights or the securities to which any rights relate may be required in order for the Company to offer such rights or such securities to Holders and to sell the securities represented by such rights, the Depositary will not distribute such rights to the Holders (i) unless and until a registration statement under the Securities Act (or other applicable law) covering such offering is in effect or (ii) unless the Company furnishes the Depositary opinion(s) of counsel for the Company in the United States and counsel to the Company in any other applicable country in which rights would be distributed, in each case satisfactory to the Depositary, to the effect that the offering and sale of such securities to Holders and Beneficial Owners are exempt from, or do not require registration under, the provisions of the Securities Act or any other applicable laws.

In the event that the Company, the Depositary or the Custodian shall be required to withhold and does withhold from any distribution of Deposited Property (including rights) an amount on account of taxes or other governmental charges, the amount distributed to the Holders of ADSs shall be reduced accordingly. In the event that the Depositary determines that any distribution of Deposited Property (including Shares and rights to subscribe therefor) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, the Depositary may dispose of all or a portion of such Deposited Property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable to pay any such taxes or charges.

There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive or exercise rights on the same terms and conditions as the holders of Shares or be able to exercise such rights. Nothing herein shall obligate the Company to file any registration statement in respect of any rights or Shares or other securities to be acquired upon the exercise of such rights.

Section 4.5 Distributions Other Than Cash, Shares or Rights to Purchase Shares.

(a) Whenever the Company intends to distribute to the holders of Deposited Securities property other than cash, Shares or rights to purchase additional Shares, the Company shall give timely notice thereof to the Depositary and shall indicate whether or not it wishes such distribution to be made to Holders of ADSs. Upon receipt of a notice indicating that the Company wishes such distribution to be made to Holders of ADSs, the Depositary shall consult with the Company, and the Company shall assist the Depositary, to determine whether such distribution to Holders is lawful and reasonably practicable. The Depositary shall not make such distribution unless (i) the Company shall have requested the Depositary to make such distribution to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7, and (iii) the Depositary shall have determined that such distribution is reasonably practicable.

(b) Upon receipt of satisfactory documentation and the request of the Company to distribute property to Holders of ADSs and after making the requisite determinations set forth in (a) above, the Depositary shall distribute the property so received to the Holders of record, as of the ADS Record Date, in proportion to the number of ADSs held by them respectively and in such manner as the Depositary may deem practicable for accomplishing such distribution (i) upon receipt of payment or net of the applicable fees and charges of, and expenses incurred by, the Depositary, and (ii) net of any applicable taxes required to be withheld. The Depositary may dispose of all or a portion of the property so distributed and deposited, in such amounts and in such manner (including public or private sale) as the Depositary may deem practicable or necessary to satisfy any taxes (including applicable interest and penalties) or other governmental charges applicable to the distribution.

(c) If (i) the Company does not request the Depositary to make such distribution to Holders or requests the Depositary not to make such distribution to Holders, (ii) the Depositary does not receive satisfactory documentation within the terms of Section 5.7, or (iii) the Depositary determines that all or a portion of such distribution is not reasonably practicable, the Depositary shall sell or cause such property to be sold in a public or private sale, at such place or places and upon such terms as it may deem practicable and shall (i) cause the proceeds of such sale, if any, to be converted into Dollars and (ii) distribute the proceeds of such conversion received by the Depositary (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) to the Holders as of the ADS Record Date upon the terms of Section 4.1. If the Depositary is unable to sell such property, the Depositary may dispose of such property for the account of the Holders in any way it deems reasonably practicable under the circumstances.

(d) Neither the Depositary nor the Company shall be liable for (i) any failure to accurately determine whether it is lawful or practicable to make the property described in this Section 4.5 available to Holders in general or any Holders in particular, nor (ii) any loss incurred in connection with the sale or disposal of such property.

Section 4.6 **Distributions with Respect to Deposited Securities in Bearer Form.** Subject to the terms of this Article IV, distributions in respect of Deposited Securities that are held by the Depositary or the Custodian in bearer form shall be made to the Depositary for the account of the respective Holders of ADS(s) with respect to which any such distribution is made upon due presentation by the Depositary or the Custodian to the Company of any relevant coupons, talons, or certificates. The Company shall promptly notify the Depositary of such distributions. The Depositary or the Custodian shall promptly present such coupons, talons or certificates, as the case may be, in connection with any such distribution.

Section 4.7 **Redemption.** If the Company intends to exercise any right of redemption in respect of any of the Deposited Securities, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the intended date of redemption which notice shall set forth the particulars of the proposed redemption. Upon timely receipt of (i) such notice and (ii) satisfactory documentation given by the Company to the Depositary within the terms of Section 5.7, and only if, after consultation between the Depositary and the Company, the Depositary shall have determined that such proposed redemption is practicable, the Depositary shall provide to each Holder a notice setting forth the intended exercise by the Company of the redemption rights and any other particulars set forth in the Company's notice to the Depositary. The Depositary shall instruct the Custodian to present to the Company the Deposited Securities in respect of which redemption rights are being exercised against payment of the applicable redemption price. Upon receipt of confirmation from the Custodian that the redemption has taken place and that funds representing the redemption price have been received, the Depositary shall convert, transfer, and distribute the proceeds (net of applicable (a) fees and charges of, and the expenses incurred by, the Depositary, and (b) taxes), retire ADSs and cancel ADRs, if applicable, upon delivery of such ADSs by Holders thereof and the terms set forth in Sections 4.1 and 6.2. If less than all outstanding Deposited Securities are redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as may be determined by the Depositary after consultation with the Company. The redemption price per ADS shall be the dollar equivalent of the per share amount received by the Depositary (adjusted to reflect the ADS(s)-to-Share(s) ratio) upon the redemption of the Deposited Securities represented by ADSs (subject to the terms of Section 4.8 and the applicable fees and charges of, and expenses incurred by, the Depositary, and applicable taxes) multiplied by the number of Deposited Securities represented by each ADS redeemed.

Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed redemption provided for in this Section 4.7, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.7, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.7 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Section 4.8 **Conversion of Foreign Currency.** Whenever the Depositary or the Custodian shall receive Foreign Currency, by way of dividends or other distributions or the net proceeds from the sale of Deposited Property, which in the judgment of the Depositary can at such time be converted on a practicable basis, by sale or in any other manner that it may determine in accordance with applicable law, into Dollars transferable to the United States and distributable to the Holders entitled thereto, the Depositary shall convert or cause to be converted, by sale or in any other manner that it may determine, such Foreign Currency into Dollars, and shall distribute such Dollars (net of any applicable fees, taxes and any expenses incurred in connection with such conversion and distribution, including, without limitation, reasonable and customary fees, taxes and any expenses incurred in complying with currency exchange controls and other governmental requirements, transaction spreads, brokerage fees, transmission fees and expenses) in accordance with the terms of the applicable sections of the Deposit Agreement. If the Depositary shall have distributed warrants or other instruments that entitle the holders thereof to such Dollars, the Depositary shall distribute such Dollars to the holders of such warrants and/or instruments upon surrender thereof for cancellation, in either case without liability for interest thereon. Such distribution may be made upon an averaged or other practicable basis without regard to any distinctions among Holders on account of any application of exchange restrictions or otherwise.

If such conversion or distribution generally or with regard to a particular Holder can be effected only with the approval or license of any government or agency thereof, the Depositary shall have authority to file such application for approval or license, if any, as it may deem desirable. In no event, however, shall the Depositary be obligated to make such a filing.

If at any time the Depositary shall determine that in its judgment the conversion of any Foreign Currency and the transfer and distribution of proceeds of such conversion received by the Depositary is not practicable or lawful, or if any approval or license of any governmental authority or agency thereof that is required for such conversion, transfer and distribution is denied or, in the opinion of the Depositary, not obtainable at a reasonable cost or within a reasonable period, the Depositary may, in its reasonable discretion, (i) make such conversion and distribution in Dollars to the Holders for whom such conversion, transfer and distribution is lawful and practicable, (ii) distribute the Foreign Currency (or an appropriate document evidencing the right to receive such Foreign Currency) to Holders for whom this is lawful and practicable, or (iii) hold (or cause the Custodian to hold) such Foreign Currency (without liability for interest thereon) for the respective accounts of the Holders entitled to receive the same.

Section 4.9 **Fixing of ADS Record Date.** Whenever (a) the Depositary shall receive notice of the fixing of a record date by the Company for the determination of holders of Deposited Securities entitled to receive any distribution (whether in cash, Shares, rights, or other distribution), (b) for any reason the Depositary causes a change in the number of Shares that are represented by each ADS, (c) the Depositary shall receive notice of any meeting of, or solicitation of consents or proxies of, holders of Shares or other Deposited Securities, or (d) the Depositary shall find it necessary or convenient in connection with the giving of any notice, solicitation of any consent or any other matter, the Depositary shall fix a record date (the "ADS Record Date") for the determination of the Holders of ADS(s) who shall be entitled to receive such distribution, to give instructions for the exercise of voting rights at any such meeting, to give or withhold such consent, to receive such notice or solicitation or to otherwise take action, or to exercise the rights of Holders with respect to such changed number of Shares represented by each ADS. The Depositary shall make reasonable efforts to establish the ADS Record Date as closely as practicable to the applicable record date for the Deposited Securities (if any) set by the Company in England and Wales and shall not announce the establishment of any ADS Record Date prior to the relevant corporate action having been made public by the Company (if such corporate action affects the Deposited Securities). Subject to applicable law and the provisions of Section 4.1 through 4.8 and to the other terms and conditions of the Deposit Agreement, only the Holders of ADSs at the close of business in New York on such ADS Record Date shall be entitled to receive such distribution, to give such voting instructions, to receive such notice or solicitation, or otherwise take action.

Section 4.10 **Voting of Deposited Securities.** As soon as practicable after receipt of notice of any meeting at which the holders of Deposited Securities are entitled to vote, or of solicitation of consents or proxies from holders of Deposited Securities, the Depositary shall fix the ADS Record Date in respect of such meeting or solicitation of consent or proxy in accordance with Section 4.9. The Depositary shall, if requested by the Company in writing in a timely manner (the Depositary having no obligation to take any further action if the request shall not have been received by the Depositary at least thirty (30) days prior to the date of such vote or meeting), at the Company's expense and provided no U.S. legal prohibitions exist, distribute as soon as practicable after receipt thereof to Holders as of the ADS Record Date: (a) such notice of meeting or solicitation of consent or proxy, (b) a statement that the Holders at the close of business on the ADS Record Date will be entitled, subject to any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of or governing the Deposited Securities (which provisions, if any, shall be summarized in pertinent part by the Company), to instruct the Depositary as to the exercise of the voting rights, if any, pertaining to the Deposited Securities represented by such Holder's ADSs, and (c) a brief statement as to the manner and timing (such timing to be determined after consultation with the Company) in which such voting instructions may be given to the Depositary or in which voting instructions may be deemed to have been given in accordance with this Section 4.10 if no instructions are received prior to the deadline set for such purposes to the Depositary to give a discretionary proxy to a person designated by the Company. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to timely request that the Depositary distribute the information as provided for in this Section 4.10, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in this Section 4.10, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in this Section 4.10 where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Notwithstanding anything contained in the Deposit Agreement or any ADR, with the Company's prior written consent, the Depositary may, to the extent not prohibited by law or regulations, or by the requirements of any stock exchange on which the ADSs may be listed, in lieu of distribution of the materials provided to the Depositary in connection with any meeting of, or solicitation of consents or proxies from, holders of Deposited Securities, distribute to the Holders a notice that provides Holders with, or otherwise publicize to Holders, instructions on how to retrieve such materials or receive such materials upon request (*e.g.*, by reference to a website containing the materials for retrieval or a contact for requesting copies of the materials).

The Depositary has been advised by the Company that the Articles of Association (as in effect on the date hereof), provide that voting at any meeting of shareholders is by show of hands unless a poll is demanded. The Depositary will not join in demanding a poll, whether or not requested to do so by Holders of ADSs. Under the Articles of Association (as in effect on the date hereof), a poll may be demanded by (i) the chairman of the general meeting; (ii) by at least two members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting; (iii) by any member of members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting and/or one tenth of the aggregate sum of the total sum paid up on all shares of the Company; or (iv) by any member or members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

Voting instructions may be given only in respect of a number of ADSs representing an integral number of Deposited Securities. Upon the timely receipt from a Holder of ADSs as of the ADS Record Date of voting instructions in the manner specified by the Depositary, the Depositary shall endeavor, insofar as practicable and permitted under any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of the Deposited Securities, to vote, or cause the Custodian to vote, the Deposited Securities (in person or by proxy) represented by such Holder's ADSs as follows: (i) in the event voting takes place at a shareholders' meeting by show of hands, the Depositary will instruct the Custodian to vote all Deposited Securities in accordance with the voting instructions received from a majority of Holders of ADSs who provided voting instructions and (ii) in the event voting takes place at a shareholders' meeting by poll, the Depositary will instruct the Custodian to vote the Deposited Securities in accordance with the voting instructions received from the Holders of ADSs. If the Depositary does not receive voting instructions from a Holder as of the ADS Record Date on or before the date established by the Depositary for such purpose, such Holder shall be deemed, and the Depositary shall deem such Holder, to have instructed the Depositary to give a discretionary proxy to a person designated by the Company to vote the Deposited Securities; provided, however, that no such discretionary proxy shall be given by the Depositary with respect to any matter to be voted upon as to which the Company informs the Depositary that (a) the Company does not wish such proxy to be given, (b) substantial opposition exists, or (c) the rights of holders of Deposited Securities may be adversely affected.

Deposited Securities represented by ADSs for which no timely voting instructions are received by the Depositary from the Holder shall not be voted (except as contemplated in this Section 4.10). Neither the Depositary nor the Custodian shall under any circumstances exercise any discretion as to voting and neither the Depositary nor the Custodian shall vote, attempt to exercise the right to vote, or in any way make use of, for purposes of establishing a quorum or otherwise, the Deposited Securities represented by ADSs, except pursuant to and in accordance with the voting instructions timely received from Holders or as otherwise contemplated herein. If the Depositary timely receives voting instructions from a Holder which fail to specify the manner in which the Depositary is to vote the Deposited Securities represented by such Holder's ADSs, the Depositary will deem such Holder (unless otherwise specified in the notice distributed to Holders) to have instructed the Depositary to vote in favor of the items set forth in such voting instructions.

Notwithstanding anything else contained herein, the Depositary shall, if so requested in writing by the Company, represent all Deposited Securities (whether or not voting instructions have been received in respect of such Deposited Securities from Holders as of the ADS Record Date) for the sole purpose of establishing quorum at a meeting of shareholders.

Notwithstanding anything else contained in the Deposit Agreement or any ADR, the Depositary shall not have any obligation to take any action with respect to any meeting, or solicitation of consents or proxies, of holders of Deposited Securities if the taking of such action would violate U.S. or English laws. The Company agrees to take any and all actions reasonably necessary and as permitted by the laws of England and Wales to enable Holders and Beneficial Owners to exercise the voting rights accruing to the Deposited Securities and to deliver to the Depositary an opinion of U.S. counsel addressing any actions requested to be taken if so reasonably requested by the Depositary.

There can be no assurance that Holders generally or any Holder in particular will receive the notice described above with sufficient time to enable the Holder to return voting instructions to the Depositary in a timely manner.

Section 4.11 **Changes Affecting Deposited Securities.** Upon any change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of Deposited Securities, or upon any recapitalization, reorganization, merger, consolidation or sale of assets affecting the Company or to which it is a party, any property which shall be received by the Depositary or the Custodian in exchange for, or in conversion of, or replacement of, or otherwise in respect of, such Deposited Securities shall, to the extent permitted by law, be treated as new Deposited Property under the Deposit Agreement, and the ADSs shall, subject to the provisions of the Deposit Agreement, any ADR(s) evidencing such ADSs and applicable law, represent the right to receive such additional or replacement Deposited Property. In giving effect to such change, split-up, cancellation, consolidation or other reclassification of Deposited Securities, recapitalization, reorganization, merger, consolidation or sale of assets, the Depositary may, with the Company's approval, and shall, if the Company shall so request, subject to the terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes) and receipt of an opinion of counsel to the Company satisfactory to the Depositary that such actions are not in violation of any applicable laws or regulations, (i) issue and deliver additional ADSs as in the case of a stock dividend on the Shares, (ii) amend the Deposit Agreement and the applicable ADRs, (iii) amend the applicable Registration Statement(s) on Form F-6 as filed with the Commission in respect of the ADSs, (iv) call for the surrender of outstanding ADRs to be exchanged for new ADRs, and (v) take such other actions as are appropriate to reflect the transaction with respect to the ADSs. The Company agrees to, jointly with the Depositary, amend the Registration Statement on Form F-6 as filed with the Commission to permit the issuance of such new form of ADRs. Notwithstanding the foregoing, in the event that any Deposited Property so received may not be lawfully distributed to some or all Holders, the Depositary may, with the Company's approval, and shall, if the Company requests, subject to receipt of an opinion of Company's counsel satisfactory to the Depositary that such action is not in violation of any applicable laws or regulations, sell such Deposited Property at public or private sale, at such place or places and upon such terms as it may deem proper and may allocate the net proceeds of such sales (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) for the account of the Holders otherwise entitled to such Deposited Property upon an averaged or other practicable basis without regard to any distinctions among such Holders and distribute the net proceeds so allocated to the extent practicable as in the case of a distribution received in cash pursuant to Section 4.1. The Depositary shall not be responsible for (i) any failure to determine that it may be lawful or practicable to make such Deposited Property available to Holders in general or to any Holder in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or (iii) any liability to the purchaser of such Deposited Property.

Section 4.12 **Available Information.** The Company is subject to the periodic reporting requirements of the Exchange Act and, accordingly, is required to file or furnish certain reports with the Commission. These reports can be retrieved from the Commission's website (www.sec.gov) and can be inspected and copied at the public reference facilities maintained by the Commission located (as of the date of the Deposit Agreement) at 100 F Street, N.E., Washington D.C. 20549.

Section 4.13 **Reports.** The Depositary shall make available for inspection by Holders at its Principal Office, as promptly as practicable after receipt thereof, any reports and communications, including any proxy soliciting materials, received from the Company which are both (a) received by the Depositary, the Custodian, or the nominee of either of them as the holder of the Deposited Property and (b) made generally available to the holders of such Deposited Property by the Company. The Depositary shall also provide or make available to Holders copies of such reports when furnished by the Company pursuant to Section 5.6.

Section 4.14 **List of Holders.** Promptly upon written request by the Company, the Depositary shall furnish to it a list, as of a recent date, of the names, addresses and holdings of ADSs of all Holders.

Section 4.15 **Taxation.** The Depositary will, and will instruct the Custodian to, forward to the Company or its agents such information from its records as the Company may reasonably request to enable the Company or its agents to file the necessary tax reports with governmental authorities or agencies. The Depositary, the Custodian or the Company and its agents may file such reports as are necessary to reduce or eliminate applicable taxes on dividends and on other distributions in respect of Deposited Property under applicable tax treaties or laws for the Holders and Beneficial Owners. In accordance with instructions from the Company and to the extent practicable, the Depositary or the Custodian will take reasonable administrative actions to obtain tax refunds, reduced withholding of tax at source on dividends and other benefits under applicable tax treaties or laws with respect to dividends and other distributions on the Deposited Property. As a condition to receiving such benefits, Holders and Beneficial Owners of ADSs may be required from time to time, and in a timely manner, to file such proof of taxpayer status, residence and beneficial ownership (as applicable), to execute such certificates and to make such representations and warranties, or to provide any other information or documents, as the Depositary or the Custodian may deem necessary or proper to fulfill the Depositary's or the Custodian's obligations under applicable law. The Depositary and the Company shall have no obligation or liability to any person if any Holder or Beneficial Owner fails to provide such information or if such information does not reach the relevant tax authorities in time for any Holder or Beneficial Owner to obtain the benefits of any tax treatment. The Holders and Beneficial Owners shall indemnify the Depositary, the Company, the Custodian and any of their respective directors, employees, agents and Affiliates against, and hold each of them harmless from, any claims by any governmental authority with respect to taxes, additions to tax, penalties or interest arising out of any refund of taxes, reduced rate of withholding at source or other tax benefit obtained for that Holder or Beneficial Owner which is required to be paid to such governmental authority.

If the Company (or any of its agents) withholds from any distribution any amount on account of taxes or governmental charges, or pays any other tax in respect of such distribution (*e.g.*, stamp duty tax, capital gains or other similar tax), the Company shall use its commercially reasonable efforts to (and shall cause such agent to) forward promptly to the Depositary information about such taxes or governmental charges withheld or paid, and, if so requested, the tax receipt (or other proof of payment to the applicable governmental authority) therefor, in each case, in a form satisfactory to the Depositary. The Depositary shall, to the extent required by U.S. law, report to Holders any taxes withheld by it or the Custodian, and, if such information is provided to it by the Company, any taxes withheld by the Company. The Depositary and the Custodian shall not be required to provide the Holders with any evidence of the remittance by the Company (or its agents) of any taxes withheld, or of the payment of taxes by the Company, except to the extent the evidence is provided by the Company to the Depositary or the Custodian, as applicable. Neither the Depositary nor the Custodian shall be liable for the failure by any Holder or Beneficial Owner to obtain the benefits of credits on the basis of non-U.S. tax paid against such Holder's or Beneficial Owner's income tax liability.

The Depositary is under no obligation to provide the Holders and Beneficial Owners with any information about the tax status of the Company except to the extent that the Company provides such information to the Depositary for distribution to the Holders and Beneficial Owners. The Depositary shall not incur any liability for any tax consequences that may be incurred by Holders and Beneficial Owners on account of their ownership of the ADSs, including without limitation, tax consequences resulting from the Company (or any of its subsidiaries) being treated as a "Passive Foreign Investment Company" (in each case as defined in the U.S. Internal Revenue Code and the regulations issued thereunder) or otherwise.

ARTICLE V

THE DEPOSITARY, THE CUSTODIAN AND THE COMPANY

Section 5.1 **Maintenance of Office and Transfer Books by the Registrar.** Until termination of the Deposit Agreement in accordance with its terms, the Registrar shall maintain in the Borough of Manhattan, the City of New York, an office and facilities for the issuance and delivery of ADSs, the acceptance for surrender of ADS(s) for the purpose of withdrawal of Deposited Securities, the registration of issuances, cancellations, transfers, combinations and split-ups of ADS(s) and, if applicable, to countersign ADRs evidencing the ADSs so issued, transferred, combined or split-up, in each case in accordance with the provisions of the Deposit Agreement.

The Registrar shall keep books for the registration of ADSs which at all reasonable times shall be open for inspection by the Company and by the Holders of such ADSs, provided that such inspection shall not be, to the Registrar's knowledge, for the purpose of communicating with Holders of such ADSs in the interest of a business or object other than the business of the Company or other than a matter related to the Deposit Agreement or the ADSs.

The Registrar may close the transfer books with respect to the ADSs, at any time or from time to time, when deemed necessary or advisable by it in good faith in connection with the performance of its duties hereunder, or at the reasonable written request of the Company subject, in all cases, to Section 7.8(a).

If any ADSs are listed on one or more stock exchanges or automated quotation systems in the United States, the Depositary shall act as Registrar or, with written notice given as promptly as practicable to the Company, appoint a Registrar or one or more co-registrars for registration of issuances, cancellations, transfers, combinations and split-ups of ADSs and, if applicable, to countersign ADRs evidencing the ADSs so issued, transferred, combined or split-up, in accordance with any requirements of such exchanges or systems. Such Registrar or co-registrars may be removed and a substitute or substitutes appointed by the Depositary, upon written notice given as promptly as practicable to the Company.

Section 5.2 **Exoneration.** Notwithstanding anything contained in the Deposit Agreement or any ADR, neither the Depositary nor the Company shall be obligated to do or perform any act which is inconsistent with the provisions of the Deposit Agreement or incur any liability (to the extent not limited by Section 7.8(b)) (i) if the Depositary, the Custodian, the Company or their respective agents shall be prevented or forbidden from, or delayed in, doing or performing any act or thing required or contemplated by the terms of the Deposit Agreement, by reason of any provision of any present or future law or regulation of the United States, England and Wales or any other country, or of any other governmental authority or regulatory authority or stock exchange, or on account of potential criminal or civil penalties or restraint, or by reason of any provision, present or future, of the Articles of Association of the Company or any provision of or governing any Deposited Securities, or by reason of any act of God or war or other circumstances beyond its control (including, without limitation, nationalization, expropriation, currency restrictions, work stoppage, strikes, civil unrest, acts of terrorism, revolutions, rebellions, explosions and computer failure), (ii) by reason of any exercise of, or failure to exercise, any discretion provided for in the Deposit Agreement or in the Articles of Association of the Company or provisions of or governing Deposited Securities, (iii) for any action or inaction in reliance upon the advice of or information from legal counsel, accountants, any person presenting Shares for deposit, any Holder, any Beneficial Owner or authorized representative thereof, or any other person believed by it in good faith to be competent to give such advice or information, (iv) for the inability by a Holder or Beneficial Owner to benefit from any distribution, offering, right or other benefit which is made available to holders of Deposited Securities but is not, under the terms of the Deposit Agreement, made available to Holders of ADSs, (v) for any action or inaction of any clearing or settlement system (and any participant thereof) for the Deposited Property or the ADSs, or (vi) for any consequential or punitive damages (including lost profits) for any breach of the terms of the Deposit Agreement.

The Depositary, its controlling persons, its agents, any Custodian and the Company, its controlling persons and its agents may rely and shall be protected in acting upon any written notice, request or other document believed by it to be genuine and to have been signed or presented by the proper party or parties.

Section 5.3 **Standard of Care.** The Company and the Depositary assume no obligation and shall not be subject to any liability under the Deposit Agreement or any ADRs to any Holder(s) or Beneficial Owner(s), except that the Company and the Depositary agree to perform their respective obligations specifically set forth in the Deposit Agreement or the applicable ADRs without negligence or bad faith.

Without limitation of the foregoing, neither the Depositary, nor the Company, nor any of their respective controlling persons, or agents, shall be under any obligation to appear in, prosecute or defend any action, suit or other proceeding in respect of any Deposited Property or in respect of the ADSs, which in its opinion may involve it in expense or liability, unless indemnity satisfactory to it against all expense (including fees and disbursements of counsel) and liability be furnished as often as may be required (and no Custodian shall be under any obligation whatsoever with respect to such proceedings, the responsibility of the Custodian being solely to the Depositary).

The Depositary and its agents shall not be liable for any failure to carry out any instructions to vote any of the Deposited Securities, or for the manner in which any vote is cast or the effect of any vote, provided that any such action or omission is in good faith and without negligence and in accordance with the terms of the Deposit Agreement. The Depositary shall not incur any liability for any failure to accurately determine that any distribution or action may be lawful or reasonably practicable, for the content of any information submitted to it by the Company for distribution to the Holders or for any inaccuracy of any translation thereof, for any investment risk associated with acquiring an interest in the Deposited Property, for the validity or worth of the Deposited Property, for the value of any Deposited Property or any distribution thereon, for any interest on Deposited Property, for any tax consequences that may result from the ownership of ADSs, Shares or other Deposited Property, for the credit-worthiness of any third party, for allowing any rights to lapse upon the terms of the Deposit Agreement, for the failure or timeliness of any notice from the Company, or for any action of or failure to act by, or any information provided or not provided by, DTC or any DTC Participant.

The Depositary shall not be liable for any acts or omissions made by a successor depositary whether in connection with a previous act or omission of the Depositary or in connection with any matter arising wholly after the removal or resignation of the Depositary, provided that in connection with the issue out of which such potential liability arises the Depositary performed its obligations without negligence or bad faith while it acted as Depositary for the Company.

Section 5.4 Resignation and Removal of the Depositary; Appointment of Successor Depositary. The Depositary may at any time resign as Depositary hereunder by written notice of resignation delivered to the Company, such resignation to be effective on the earlier of (i) the 90th day after delivery thereof to the Company (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2), or (ii) the appointment by the Company of a successor depositary and its acceptance of such appointment as hereinafter provided.

The Depositary may at any time be removed by the Company by written notice of such removal, which removal shall be effective on the later of (i) the 90th day after delivery thereof to the Depositary (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2), or (ii) upon the appointment by the Company of a successor depositary and its acceptance of such appointment as hereinafter provided.

In case at any time the Depositary acting hereunder shall resign or be removed, the Company shall use its best efforts to appoint a successor depositary, which shall be a bank or trust company having an office in the Borough of Manhattan, the City of New York. Every successor depositary shall be required by the Company to execute and deliver to its predecessor and to the Company an instrument in writing accepting its appointment hereunder, and thereupon such successor depositary, without any further act or deed (except as required by applicable law), shall become fully vested with all the rights, powers, duties and obligations of its predecessor (other than as contemplated in Sections 5.8 and 5.9). The predecessor depositary, upon payment of all sums due it and on the written request of the Company, shall, (i) execute and deliver an instrument transferring to such successor all rights and powers of such predecessor hereunder (other than as contemplated in Sections 5.8 and 5.9), (ii) duly assign, transfer and deliver all of the Depositary's right, title and interest to the Deposited Property to such successor, and (iii) deliver to such successor a list of the Holders of all outstanding ADSs and such other information relating to ADSs and Holders thereof as the successor may reasonably request. Any such successor depositary shall promptly provide notice of its appointment to such Holders.

Any entity into or with which the Depositary may be merged or consolidated shall be the successor of the Depositary without the execution or filing of any document or any further act.

Section 5.5 **The Custodian.** The Depositary has initially appointed Citibank, N.A. (London) as Custodian for the purpose of the Deposit Agreement. The Custodian or its successors in acting hereunder shall be subject at all times and in all respects to the direction of the Depositary for the Deposited Property for which the Custodian acts as custodian and shall be responsible solely to it. If any Custodian resigns or is discharged from its duties hereunder with respect to any Deposited Property and no other Custodian has previously been appointed hereunder, the Depositary shall promptly appoint a substitute custodian. The Depositary shall require such resigning or discharged Custodian to Deliver, or cause the Delivery of, the Deposited Property held by it, together with all such records maintained by it as Custodian with respect to such Deposited Property as the Depositary may request, to the Custodian designated by the Depositary. Whenever the Depositary determines, in its discretion, that it is appropriate to do so, it may appoint an additional custodian with respect to any Deposited Property, or discharge the Custodian with respect to any Deposited Property and appoint a substitute custodian, which shall thereafter be Custodian hereunder with respect to the Deposited Property. Immediately upon any such change, the Depositary shall give notice thereof in writing to all Holders of ADSs, each other Custodian and the Company.

Citibank, N.A. may at any time act as Custodian of the Deposited Property pursuant to the Deposit Agreement, in which case any reference to Custodian shall mean Citibank, N.A. solely in its capacity as Custodian pursuant to the Deposit Agreement and the Depositary shall promptly give notice thereof to the Company. Notwithstanding anything contained in the Deposit Agreement or any ADR, the Depositary shall not be obligated to give notice to any Holders of ADSs or any other Custodian of its acting as Custodian pursuant to the Deposit Agreement.

Upon the appointment of any successor depositary, any Custodian then acting hereunder shall, unless otherwise instructed by the Depositary, continue to be the Custodian of the Deposited Property without any further act or writing, and shall be subject to the direction of the successor depositary. The successor depositary so appointed shall, nevertheless, on the written request of any Custodian, execute and deliver to such Custodian all such instruments as may be proper to give to such Custodian full and complete power and authority to act on the direction of such successor depositary.

Section 5.6 **Notices and Reports.** On or before the first date on which the Company gives notice, by publication or otherwise, of any meeting of holders of Shares or other Deposited Securities, or of any adjourned meeting of such holders, or of the taking of any action by such holders other than at a meeting, or of the taking of any action in respect of any cash or other distributions or the offering of any rights in respect of Deposited Securities, the Company shall transmit to the Depositary and the Custodian a copy of the notice thereof in the English language but otherwise in the form given or to be given to holders of Shares or other Deposited Securities. The Company shall also furnish to the Custodian and the Depositary a summary, in English, of any applicable provisions or proposed provisions of the Articles of Association of the Company that may be relevant or pertain to such notice of meeting or be the subject of a vote thereat.

The Company will also transmit to the Depositary (a) an English language version of the other notices, reports and communications which are made generally available by the Company to holders of its Shares or other Deposited Securities and (b) the English-language versions of the Company's annual and semi-annual reports prepared in accordance with the applicable requirements of the Commission. The Depositary shall arrange, at the request of the Company and at the Company's expense, to provide copies thereof to all Holders or make such notices, reports and other communications available to all Holders on a basis similar to that for holders of Shares or other Deposited Securities or on such other basis as the Company may advise the Depositary or as may be required by any applicable law, regulation or stock exchange requirement. The Company has delivered to the Depositary and the Custodian a copy of the Company's Articles of Association along with the provisions of or governing the Shares and any other Deposited Securities issued by the Company in connection with such Shares, and promptly upon any amendment thereto or change therein, the Company shall deliver to the Depositary and the Custodian a copy of such amendment thereto or change therein to the extent such amendment or change is not available on the Company's website or is not otherwise publicly available. The Depositary may rely upon such copy for all purposes of the Deposit Agreement.

The Depositary will, at the expense of the Company, make available a copy of any such notices, reports or communications issued by the Company and delivered to the Depositary for inspection by the Holders of the ADSs at the Depositary's Principal Office, at the office of the Custodian and at any other designated transfer office.

Section 5.7 **Issuance of Additional Shares, ADSs etc.** The Company agrees that in the event it or any of its Affiliates proposes (i) an issuance, sale or distribution of additional Shares, (ii) an offering of rights to subscribe for Shares or other Deposited Securities, (iii) an issuance or assumption of securities convertible into or exchangeable for Shares, (iv) an issuance of rights to subscribe for securities convertible into or exchangeable for Shares, (v) an elective dividend of cash or Shares, (vi) a redemption of Deposited Securities, (vii) a meeting of holders of Deposited Securities, or solicitation of consents or proxies, relating to any reclassification of securities, merger or consolidation or transfer of assets, (viii) any assumption, reclassification, recapitalization, reorganization, merger, consolidation or sale of assets which affects the Deposited Securities, or (ix) a distribution of securities other than Shares, it will obtain U.S. legal advice and take all steps necessary to ensure that the application of the proposed transaction to Holders and Beneficial Owners does not violate the registration provisions of the Securities Act, or any other applicable laws (including, without limitation, the Investment Company Act of 1940, as amended, the Exchange Act and the securities laws of the states of the U.S.). In support of the foregoing, the Company will furnish to the Depositary (a) a written opinion of U.S. counsel (reasonably satisfactory to the Depositary) stating whether such transaction (1) requires a registration statement under the Securities Act to be in effect or (2) is exempt from the registration requirements of the Securities Act and (b) an opinion of English counsel stating that (1) making the transaction available to Holders and Beneficial Owners does not violate the laws or regulations of England and Wales and (2) all requisite regulatory consents and approvals have been obtained in England and Wales. If the filing of a registration statement is required, the Depositary shall not have any obligation to proceed with the transaction unless it shall have received evidence reasonably satisfactory to it that such registration statement has been declared effective. If, being advised by counsel, the Company determines that a transaction is required to be registered under

the Securities Act, the Company will either (i) register such transaction to the extent necessary, (ii) alter the terms of the transaction to avoid the registration requirements of the Securities Act or (iii) direct the Depositary to take specific measures, in each case as contemplated in the Deposit Agreement, to prevent such transaction from violating the registration requirements of the Securities Act. The Company agrees with the Depositary that neither the Company nor any of its Affiliates will at any time (i) deposit any Shares or other Deposited Securities, either upon original issuance or upon a sale of Shares or other Deposited Securities previously issued and reacquired by the Company or by any such Affiliate, or (ii) issue additional Shares, rights to subscribe for such Shares, securities convertible into or exchangeable for Shares or rights to subscribe for such securities or distribute securities other than Shares, unless such transaction and the securities issuable in such transaction do not violate the registration provisions of the Securities Act, or any other applicable laws (including, without limitation, the Investment Company Act of 1940, as amended, the Exchange Act and the securities laws of the states of the U.S.).

Notwithstanding anything else contained in the Deposit Agreement, nothing in the Deposit Agreement shall be deemed to obligate the Company to file any registration statement in respect of any proposed transaction.

Section 5.8 **Indemnification.** The Depositary agrees to indemnify the Company and its directors, officers, employees, agents and Affiliates against, and hold each of them harmless from, any direct loss, liability, tax, charge or expense of any kind whatsoever (including, but not limited to, the reasonable fees and expenses of counsel) which may arise out of acts performed or omitted by the Depositary under the terms hereof due to the negligence or bad faith of the Depositary.

The Company agrees to indemnify the Depositary, the Custodian and any of their respective directors, officers, employees, agents and Affiliates against, and hold each of them harmless from, any direct loss, liability, tax, charge or expense of any kind whatsoever (including, but not limited to, the reasonable fees and expenses of counsel) that may arise (a) out of, or in connection with, any offer, issuance, sale, resale, transfer, deposit or withdrawal of ADRs, ADSs, the Shares, or other Deposited Securities, as the case may be, to the extent it is not unlawful for the Company to indemnify such person at such time under applicable English law, (b) out of, or as a result of, any offering documents in respect thereof or (c) out of acts performed or omitted, including, but not limited to, any delivery by the Depositary on behalf of the Company of information regarding the Company, in connection with the Deposit Agreement, any ancillary or supplemental agreement entered into between the Company and the Depositary, the ADRs, the ADSs, the Shares, or any Deposited Property, in any such case (i) by the Depositary, the Custodian or any of their respective directors, officers, employees, agents and Affiliates, except to the extent such loss, liability, tax, charge or expense is due to the fraud, negligence or bad faith of any of them, or (ii) by the Company or any of its directors, officers, employees, agents and Affiliates; provided, however, that the Company shall not be liable for any fees, charges or expenses payable by third party Holders or Beneficial Owners under this Deposit Agreement. The Company shall not indemnify the Depositary or the Custodian (for so long as the Custodian is a branch of Citibank, N.A.) against any liability or expense arising out of information relating to the Depositary or such Custodian, as the case may be, furnished in a signed writing to the Company, executed by the Depositary expressly for use in any registration statement, prospectus or preliminary prospectus relating to any Deposited Securities represented by the ADSs.

The obligations set forth in this Section shall survive the termination of the Deposit Agreement and the succession or substitution of any party hereto.

Any person seeking indemnification hereunder (an "indemnified person") shall notify the person from whom it is seeking indemnification (the "indemnifying person") of the commencement of any indemnifiable action or claim promptly after such indemnified person becomes aware of such commencement (provided that the failure to make such notification shall not affect such indemnified person's rights to seek indemnification except to the extent the indemnifying person is materially prejudiced by such failure) and shall consult in good faith with the indemnifying person as to the conduct of the defense of such action or claim that may give rise to an indemnity hereunder, which defense shall be reasonable in the circumstances. No indemnified person shall compromise or settle any action or claim that may give rise to an indemnity hereunder without the consent of the indemnifying person, which consent shall not be unreasonably withheld.

Section 5.9 **ADS Fees and Charges.** The Company, the Holders, the Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with the issuance and cancellation of ADSs, and persons receiving ADSs upon issuance or for whom ADSs are being cancelled shall be required to pay the ADS fees and charges identified as payable by them respectively in the ADS fee schedule attached hereto as Exhibit B. All ADS fees and charges so payable may be deducted from distributions or must be remitted to the Depositary, or its designee, may, at any time and from time to time, be changed by agreement between the Depositary and the Company, but, in the case of ADS fees and charges payable by Holders and Beneficial Owners, only in the manner contemplated in Section 6.1. The Depositary shall provide, without charge, a copy of its latest ADS fee schedule to anyone upon request.

ADS fees and charges payable upon (i) the issuance of ADSs and (ii) the cancellation of ADSs will be payable by the person for whom the ADSs are so issued by the Depositary (in the case of ADS issuances) and by the person for whom ADSs are being cancelled by the Depositary (in the case of ADS cancellations). In the case of ADSs issued by the Depositary into DTC or presented to the Depositary via DTC, the ADS issuance and cancellation fees and charges will be payable by the DTC Participant(s) receiving the ADSs from the Depositary or the DTC Participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the Beneficial Owner(s) and will be charged by the DTC Participant(s) to the account(s) of the applicable Beneficial Owner(s) in accordance with the procedures and practices of the DTC Participant(s) as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are payable by Holders as of the applicable ADS Record Date established by the Depositary. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, the applicable Holders as of the ADS Record Date established by the Depositary will be invoiced for the amount of the ADS fees and charges and such ADS fees may be deducted from distributions made to Holders. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC Participants in accordance with the procedures and practices prescribed by DTC from time to time and the DTC Participants in turn charge the amount of such ADS fees and charges to the Beneficial Owners for whom they hold ADSs.

The Depositary may reimburse the Company for certain expenses incurred by the Company in respect of the ADR program established pursuant to the Deposit Agreement, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as the Company and the Depositary agree from time to time. The Company shall pay to the Depositary such fees and charges, and reimburse the Depositary for such out-of-pocket expenses, as the Depositary and the Company may agree from time to time. Responsibility for payment of such fees, charges and reimbursements may from time to time be changed by agreement between the Company and the Depositary. Unless otherwise agreed, the Depositary shall present its statement for such fees, charges and reimbursements to the Company once every three months. The charges and expenses of the Custodian are for the sole account of the Depositary.

The obligations of Holders and Beneficial Owners to pay ADS fees and charges shall survive the termination of the Deposit Agreement. As to any Depositary, upon the resignation or removal of such Depositary as described in Section 5.4, the right to collect ADS fees and charges shall extend for those ADS fees and charges incurred prior to the effectiveness of such resignation or removal.

Section 5.10 **Restricted Securities Owners.** The Company agrees to advise in writing each of the persons or entities who, to the knowledge of the Company, holds Restricted Securities that such Restricted Securities are ineligible for deposit hereunder (except under the circumstances contemplated in Section 2.14) and, to the extent practicable, shall require each of such persons to represent in writing that such person will not deposit Restricted Securities hereunder (except under the circumstances contemplated in Section 2.14).

ARTICLE VI

AMENDMENT AND TERMINATION

Section 6.1 **Amendment/Supplement.** Subject to the terms and conditions of this Section 6.1 and applicable law, the ADRs outstanding at any time, the provisions of the Deposit Agreement and the form of ADR attached hereto and to be issued under the terms hereof may at any time and from time to time be amended or supplemented by written agreement between the Company and the Depositary in any respect which they may deem necessary or desirable without the prior written consent of the Holders or Beneficial Owners. Any amendment or supplement which shall impose or increase any fees or charges (other than charges in connection with foreign exchange control regulations, and taxes and other governmental charges, delivery and other such expenses), or which shall otherwise materially prejudice any substantial existing right of Holders or Beneficial Owners, shall not, however, become effective as to outstanding ADSs until the expiration of thirty (30) days after notice of such amendment or supplement shall have been given to the Holders of outstanding ADSs. Notice of any amendment to the Deposit Agreement or any ADR shall not need to describe in detail the specific amendments effectuated thereby, and failure to describe the specific amendments in any such notice shall not render such notice invalid, provided, however, that, in each such case, the notice given to the Holders identifies a means for Holders and Beneficial Owners to retrieve or receive the text of such amendment (*e.g.*, upon retrieval from the Commission's, the Depositary's or the Company's website or upon request from the Depositary). The parties hereto agree that any amendments or supplements which (i) are reasonably necessary (as agreed by the Company and the Depositary) in order for (a) the ADSs to be registered on Form F-6 under the Securities Act or (b) the ADSs to be settled solely in electronic book-entry form and (ii) do not in either such case impose or increase any fees or charges to be borne by Holders, shall be deemed not to materially prejudice any substantial rights of Holders or Beneficial Owners. Every Holder and Beneficial Owner at the time any amendment or supplement so becomes effective shall be deemed, by continuing to hold such ADSs, to consent and agree to such amendment or supplement and to be bound by the Deposit Agreement and the ADR, if applicable, as amended or supplemented thereby. In no event shall any amendment or supplement impair the right of the Holder to surrender such ADS and receive therefor the Deposited Securities represented thereby, except in order to comply with mandatory provisions of applicable law. Notwithstanding the foregoing, if any governmental body should adopt new laws, rules or regulations which would require an amendment of, or supplement to, the Deposit Agreement to ensure compliance therewith, the Company and the Depositary may amend or supplement the Deposit Agreement and any ADRs at any time in accordance with such changed laws, rules or regulations. Such amendment or supplement to the Deposit Agreement and any ADRs in such circumstances may become effective before a notice of such amendment or supplement is given to Holders or within any other period of time as required for compliance with such laws, rules or regulations.

Section 6.2 Termination. The Depositary shall, at any time at the written direction of the Company, terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. If ninety (90) days shall have expired after (i) the Depositary shall have delivered to the Company a written notice of its election to resign, or (ii) the Company shall have delivered to the Depositary a written notice of the removal of the Depositary, and, in either case, a successor depositary shall not have been appointed and accepted its appointment as provided in Section 5.4 of the Deposit Agreement, the Depositary may terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. The date so fixed for termination of the Deposit Agreement in any termination notice so distributed by the Depositary to the Holders of ADSs is referred to as the "Termination Date". Until the Termination Date, the Depositary shall continue to perform all of its obligations under the Deposit Agreement, and the Holders and Beneficial Owners will be entitled to all of their rights under the Deposit Agreement.

If any ADSs shall remain outstanding after the Termination Date, the Registrar and the Depositary shall not, after the Termination Date, have any obligation to perform any further acts under the Deposit Agreement, except that the Depositary shall, subject, in each case, to the terms and conditions of the Deposit Agreement, continue to (i) collect dividends and other distributions pertaining to Deposited Securities, (ii) sell Deposited Property received in respect of Deposited Securities, (iii) deliver Deposited Securities, together with any dividends or other distributions received with respect thereto and the net proceeds of the sale of any other Deposited Property, in exchange for ADSs surrendered to the Depositary (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (iv) take such actions as may be required under applicable law in connection with its role as Depositary under the Deposit Agreement.

At any time after the Termination Date, the Depositary may sell the Deposited Property then held under the Deposit Agreement and shall after such sale hold un-invested the net proceeds of such sale, together with any other cash then held by it under the Deposit Agreement, in an un-segregated account and without liability for interest, for the pro rata benefit of the Holders whose ADSs have not theretofore been surrendered. After making such sale, the Depositary shall be discharged from all obligations under the Deposit Agreement except (i) to account for such net proceeds and other cash (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (ii) as may be required at law in connection with the termination of the Deposit Agreement. After the Termination Date, the Company shall be discharged from all obligations under the Deposit Agreement, except for its obligations to the Depositary under Sections 5.8, 5.9 and 7.6 of the Deposit Agreement. The obligations under the terms of the Deposit Agreement of Holders and Beneficial Owners of ADSs outstanding as of the Termination Date shall survive the Termination Date and shall be discharged only when the applicable ADSs are presented by their Holders to the Depositary for cancellation under the terms of the Deposit Agreement (except as specifically provided in the Deposit Agreement).

Notwithstanding anything contained in the Deposit Agreement or any ADR, in connection with the termination of the Deposit Agreement, the Depositary may, independently and without the need for any action by the Company, make available to Holders of ADSs a means to withdraw the Deposited Securities represented by their ADSs and to direct the deposit of such Deposited Securities into an unsponsored American depositary shares program established by the Depositary, upon such terms and conditions as the Depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored American depositary shares program under the Securities Act, and to receipt by the Depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the Depositary.

ARTICLE VII

MISCELLANEOUS

Section 7.1 **Counterparts.** The Deposit Agreement may be executed in any number of counterparts, each of which shall be deemed an original and all of such counterparts together shall constitute one and the same agreement. Copies of the Deposit Agreement shall be maintained with the Depositary and shall be open to inspection by any Holder during business hours.

Section 7.2 **No Third-Party Beneficiaries/Acknowledgments.** The Deposit Agreement is for the exclusive benefit of the parties hereto (and their successors) and shall not be deemed to give any legal or equitable right, remedy or claim whatsoever to any other person, except to the extent specifically set forth in the Deposit Agreement. Nothing in the Deposit Agreement shall be deemed to give rise to a partnership or joint venture among the parties nor establish a fiduciary or similar relationship among the parties. The parties hereto acknowledge and agree that (i) Citibank and its Affiliates may at any time have multiple banking relationships with the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (ii) Citibank and its Affiliates may own and deal in any class of securities of the Company and its Affiliates and in ADSs, and may be engaged at any time in transactions in which parties adverse to the Company, the Holders, the Beneficial Owners or their respective Affiliates may have interests, (iii) the Depositary and its Affiliates may from time to time have in their possession non-public information about the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (iv) nothing contained in the Deposit Agreement shall (a) preclude Citibank or any of its Affiliates from engaging in such transactions or establishing or maintaining such relationships, (b) obligate Citibank or any of its Affiliates to disclose such information, transactions or relationships, or to account for any profit made or payment received in such transactions or relationships, (v) the Depositary shall not be deemed to have knowledge of any information any other division of Citibank or any of its Affiliates may have about the Company, the Holders, the Beneficial Owners, or any of their respective Affiliates, and (vi) the Company, the Depositary, the Custodian and their respective agents and controlling persons may be subject to the laws and regulations of jurisdictions other than the United States, England, and the authority of courts and regulatory authorities of such other jurisdictions, and, consequently, the requirements and the limitations of such other laws and regulations, and the decisions and orders of such other courts and regulatory authorities, may affect the rights and obligations of the parties to the Deposit Agreement.

Section 7.3 **Severability.** In case any one or more of the provisions contained in the Deposit Agreement or in the ADRs should be or become invalid, illegal or unenforceable in any respect, the validity, legality and enforceability of the remaining provisions contained herein or therein shall in no way be affected, prejudiced or disturbed thereby.

The Depositary may execute transactions contemplated herein (e.g., foreign currency conversions, and sales of Deposited Property) through one or more divisions of Citibank or through one or more Citibank Affiliates, and any such entity may act as principal for its own account and not as agent, advisor, broker or fiduciary on behalf of any other person and may earn and retain revenue from such transactions, including, without, without limitation, transaction spreads, commissions, etc. The Depositary does not guarantee or represent that the price or rate obtained in any such transaction, or the method for obtaining such price or rate, will be the most favorable that could be obtained at that time.

Section 7.4 **Holders and Beneficial Owners as Parties; Binding Effect.** The Holders and Beneficial Owners from time to time of ADSs issued hereunder shall be parties to the Deposit Agreement and shall be bound by all of the terms and conditions hereof and of any ADR evidencing their ADSs by acceptance thereof or any beneficial interest therein.

Section 7.5 **Notices.** Any and all notices to be given to the Company shall be deemed to have been duly given if personally delivered or sent by mail, air courier or cable, telex or facsimile transmission, confirmed by letter personally delivered or sent by mail or air courier, addressed to Orchard Therapeutics plc, 108 Cannon Street, London EC4N 6EU, United Kingdom, Attention: John Ilett, General Counsel & Company Secretary, or to any other address which the Company may specify in writing to the Depositary.

Any and all notices to be given to the Depositary shall be deemed to have been duly given if personally delivered or sent by mail, air courier or cable, telex or facsimile transmission, confirmed by letter personally delivered or sent by mail or air courier, addressed to Citibank, N.A., 388 Greenwich Street, New York, New York 10013, U.S.A., Attention: Depositary Receipts Department, or to any other address which the Depositary may specify in writing to the Company.

Any and all notices to be given to any Holder shall be deemed to have been duly given **(a)** if personally delivered or sent by mail or cable, telex or facsimile transmission, confirmed by letter, addressed to such Holder at the address of such Holder as it appears on the books of the Depositary or, if such Holder shall have filed with the Depositary a request that notices intended for such Holder be mailed to some other address, at the address specified in such request, or **(b)** if a Holder shall have designated such means of notification as an acceptable means of notification under the terms of the Deposit Agreement, by means of electronic messaging addressed for delivery to the e-mail address designated by the Holder for such purpose. Notice to Holders shall be deemed to be notice to Beneficial Owners for all purposes of the Deposit Agreement. Failure to notify a Holder or any defect in the notification to a Holder shall not affect the sufficiency of notification to other Holders or to the Beneficial Owners of ADSs held by such other Holders. Any notices given to DTC under the terms of the Deposit Agreement shall (unless otherwise specified by the Depositary) constitute notice to the DTC Participants who hold as the ADSs in their DTC accounts and to the Beneficial Owners of such ADSs.

Delivery of a notice sent by mail, air courier or cable, telex or facsimile transmission shall be deemed to be effective at the time when a duly addressed letter containing the same (or a confirmation thereof in the case of a cable, telex or facsimile transmission) is deposited, postage prepaid, in a post-office letter box or delivered to an air courier service, without regard for the actual receipt or time of actual receipt thereof by a Holder. The Depositary or the Company may, however, act upon any cable, telex or facsimile transmission received by it from any Holder, the Custodian, the Depositary, or the Company, notwithstanding that such cable, telex or facsimile transmission shall not be subsequently confirmed by letter.

Delivery of a notice by means of electronic messaging shall be deemed to be effective at the time of the initiation of the transmission by the sender (as shown on the sender's records), notwithstanding that the intended recipient retrieves the message at a later date, fails to retrieve such message, or fails to receive such notice on account of its failure to maintain the designated e-mail address, its failure to designate a substitute e-mail address or for any other reason.

Section 7.6 **Governing Law and Jurisdiction.** The Deposit Agreement and the ADRs shall be interpreted in accordance with, and all rights hereunder and thereunder and provisions hereof and thereof shall be governed by, the laws of the State of New York applicable to contracts made and to be wholly performed in that State. Notwithstanding anything contained in the Deposit Agreement, any ADR or any present or future provisions of the laws of the State of New York, the rights of holders of Shares and of any other Deposited Securities and the obligations and duties of the Company in respect of the holders of Shares and other Deposited Securities, as such, shall be governed by the laws of England and Wales (or, if applicable, such other laws as may govern the Deposited Securities).

Except as set forth in the following paragraph of this Section 7.6, the Company and the Depositary agree that the federal or state courts in the City of New York shall have jurisdiction to hear and determine any suit, action or proceeding and to settle any dispute between them that may arise out of or in connection with the Deposit Agreement and, for such purposes, each irrevocably submits to the non-exclusive jurisdiction of such courts. The Company hereby irrevocably designates, appoints and empowers Cogency Global Inc. (the "Agent") now at 10 East 40th Street 10th Floor, New York, New York 10016, as its authorized agent to receive and accept for and on its behalf, and on behalf of its properties, assets and revenues, service by mail of any and all legal process, summons, notices and documents that may be served in any suit, action or proceeding brought against the Company in any federal or state court as described in the preceding sentence or in the next paragraph of this Section 7.6. If for any reason the Agent shall cease to be available to act as such, the Company agrees to designate a new agent in New York on the terms and for the purposes of this Section 7.6 reasonably satisfactory to the Depositary. The Company further hereby irrevocably consents and agrees to the service of any and all legal process, summons, notices and documents in any suit, action or proceeding against the Company, by service by mail of a copy thereof upon the Agent (whether or not the appointment of such Agent shall for any reason prove to be ineffective or such Agent shall fail to accept or acknowledge such service), with a copy mailed to the Company by registered or certified air mail, postage prepaid, to its address provided in Section 7.5. The Company agrees that the failure of the Agent to give any notice of such service to it shall not impair or affect in any way the validity of such service or any judgment rendered in any action or proceeding based thereon.

Notwithstanding the foregoing, the Depositary and the Company unconditionally agree that in the event that a Holder or Beneficial Owner brings a suit, action or proceeding against (a) the Company, (b) the Depositary in its capacity as Depositary under the Deposit Agreement or (c) against both the Company and the Depositary, in any such case, in any state or federal court of the United States, and the Depositary or the Company have any claim, for indemnification or otherwise, against each other arising out of the subject matter of such suit, action or proceeding, then the Company and the Depositary may pursue such claim against each other in the state or federal court in the United States in which such suit, action, or proceeding is pending and, for such purposes, the Company and the Depositary irrevocably submit to the non-exclusive jurisdiction of such courts. The Company agrees that service of process upon the Agent in the manner set forth in the preceding paragraph shall be effective service upon it for any suit, action or proceeding brought against it as described in this paragraph.

The Company irrevocably and unconditionally waives, to the fullest extent permitted by law, any objection that it may now or hereafter have to the laying of venue of any actions, suits or proceedings brought in any court as provided in this Section 7.6, and hereby further irrevocably and unconditionally waives and agrees not to plead or claim in any such court that any such action, suit or proceeding brought in any such court has been brought in an inconvenient forum.

The Company irrevocably and unconditionally waives, to the fullest extent permitted by law, and agrees not to plead or claim, any right of immunity from legal action, suit or proceeding, from setoff or counterclaim, from the jurisdiction of any court, from service of process, from attachment upon or prior to judgment, from attachment in aid of execution or judgment, from execution of judgment, or from any other legal process or proceeding for the giving of any relief or for the enforcement of any judgment, and consents to such relief and enforcement against it, its assets and its revenues in any jurisdiction, in each case with respect to any matter arising out of, or in connection with, the Deposit Agreement, any ADR or the Deposited Property.

EACH OF THE PARTIES TO THE DEPOSIT AGREEMENT (INCLUDING, WITHOUT LIMITATION, EACH HOLDER AND BENEFICIAL OWNER) IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING AGAINST THE COMPANY AND/OR THE DEPOSITARY ARISING OUT OF, OR RELATING TO, THE DEPOSIT AGREEMENT, ANY ADR AND ANY TRANSACTIONS CONTEMPLATED THEREIN (WHETHER BASED ON CONTRACT, TORT, COMMON LAW OR OTHERWISE).

The provisions of this Section 7.6 shall survive any termination of the Deposit Agreement, in whole or in part.

Section 7.7 Assignment. Subject to the provisions of Section 5.4, the Deposit Agreement may not be assigned by either the Company or the Depositary.

Section 7.8 Compliance with, and No Disclaimer under, U.S. Securities Laws.

(a) Notwithstanding anything in the Deposit Agreement to the contrary, the withdrawal or delivery of Deposited Securities will not be suspended by the Company or the Depositary except as would be permitted by Instruction I.A.(1) of the General Instructions to Form F-6 Registration Statement, as amended from time to time, under the Securities Act.

(b) Each of the parties to the Deposit Agreement (including, without limitation, each Holder and Beneficial Owner) acknowledges and agrees that no provision of the Deposit Agreement or any ADR shall, or shall be deemed to, disclaim any liability under the Securities Act or the Exchange Act, in each case to the extent established under applicable U.S. laws.

Section 7.9 English Law References. Any summary of English laws and regulations and of the terms of the Company's Articles of Association set forth in the Deposit Agreement have been provided by the Company solely for the convenience of Holders, Beneficial Owners and the Depositary. While such summaries are believed by the Company to be accurate as of the date of the Deposit Agreement, (i) they are summaries and as such may not include all aspects of the materials summarized applicable to a Holder or Beneficial Owner, and (ii) these laws and regulations and the Company's Articles of Association may change after the date of the Deposit Agreement. Neither the Depositary nor the Company has any obligation under the terms of the Deposit Agreement to update any such summaries.

Section 7.10 Titles and References.

(a) **Deposit Agreement.** All references in the Deposit Agreement to exhibits, articles, sections, subsections, and other subdivisions refer to the exhibits, articles, sections, subsections and other subdivisions of the Deposit Agreement unless expressly provided otherwise. The words "the Deposit Agreement", "herein", "hereof", "hereby", "hereunder", and words of similar import refer to the Deposit Agreement as a whole as in effect at the relevant time between the Company, the Depositary and the Holders and Beneficial Owners of ADSs and not to any particular subdivision unless expressly so limited. Pronouns in masculine, feminine and neuter gender shall be construed to include any other gender, and words in the singular form shall be construed to include the plural and *vice versa* unless the context otherwise requires. Titles to sections of the Deposit Agreement are included for convenience only and shall be disregarded in construing the language contained in the Deposit Agreement. References to "applicable laws and regulations" shall refer to laws and regulations applicable to ADRs, ADSs or Deposited Property as in effect at the relevant time of determination, unless otherwise required by law or regulation.

(b) **ADRs.** All references in any ADR(s) to paragraphs, exhibits, articles, sections, subsections, and other subdivisions refer to the paragraphs, exhibits, articles, sections, subsections and other subdivisions of the ADR(s) in question unless expressly provided otherwise. The words "the Receipt", "the ADR", "herein", "hereof", "hereby", "hereunder", and words of similar import used in any ADR refer to the ADR as a whole and as in effect at the relevant time, and not to any particular subdivision unless expressly so limited. Pronouns in masculine, feminine and neuter gender in any ADR shall be construed to include any other gender, and words in the singular form shall be construed to include the plural and *vice versa* unless the context otherwise requires. Titles to paragraphs of any ADR are included for convenience only and shall be disregarded in construing the language contained in the ADR. References to "applicable laws and regulations" shall refer to laws and regulations applicable to the Company, the Depositary, the Custodian, their agents and controlling persons, the ADRs, the ADSs and the Deposited Property as in effect at the relevant time of determination, unless otherwise required by law or regulation.

[*Signature Page Follows*]

IN WITNESS WHEREOF, ORCHARD THERAPEUTICS PLC and CITIBANK, N.A. have duly executed the Deposit Agreement as of the day and year first above set forth and all Holders and Beneficial Owners shall become parties hereto upon acceptance by them of ADSs issued in accordance with the terms hereof, or upon acquisition of any beneficial interest therein.

ORCHARD THERAPEUTICS PLC

By: /s/ Mark Rothera
Name: Mark Rothera
Title: Chief Executive Officer

CITIBANK, N.A.

By: /s/ Keith Galfo
Name: Keith Galfo
Title: Vice President

EXHIBIT A

FORM OF ADR

Number _____ CUSIP NUMBER: _____

American Depositary Shares (each American Depositary Share representing the right to receive one (1) fully paid ordinary share)

AMERICAN DEPOSITARY RECEIPT

for

AMERICAN DEPOSITARY SHARES

representing

DEPOSITED ORDINARY SHARES

of

ORCHARD THERAPEUTICS PLC

(Incorporated under the laws of England and Wales)

CITIBANK, N.A., a national banking association organized and existing under the laws of the United States of America, as depositary (the "Depositary"), hereby certifies that _____is the owner of _____ American Depositary Shares (hereinafter "ADS") representing deposited ordinary shares, including evidence of rights to receive such ordinary shares (the "Shares"), of Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales (the "Company"). As of the date of issuance of this ADR, each ADS represents the right to receive one (1) Share deposited under the Deposit Agreement (as hereinafter defined) with the Custodian, which at the date of issuance of this ADR is Citibank, N.A. (London) (the "Custodian"). The ADS(s)-to-Share(s) ratio is subject to amendment as provided in Articles IV and VI of the Deposit Agreement. The Depositary's Principal Office is located at 388 Greenwich Street, New York, New York 10013, U.S.A.

(1) **The Deposit Agreement.** This American Depositary Receipt is one of an issue of American Depositary Receipts ("ADRs"), all issued and to be issued upon the terms and conditions set forth in the Deposit Agreement, dated as of November 2, 2018 (as amended and supplemented from time to time, the "Deposit Agreement"), by and among the Company, the Depositary, and all Holders and Beneficial Owners from time to time of ADSs issued thereunder. The Deposit Agreement sets forth the rights and obligations of Holders and Beneficial Owners of ADSs and the rights and duties of the Depositary in respect of the Shares deposited thereunder and any and all other Deposited Property (as defined in the Deposit Agreement) from time to time received and held on deposit in respect of the ADSs. Copies of the Deposit Agreement are on file at the Principal Office of the Depositary and with the Custodian. Each Holder and each Beneficial Owner, upon acceptance of any ADSs (or any interest therein) issued in accordance with the terms and conditions of the Deposit Agreement, shall be deemed for all purposes to (a) be a party to and bound by the terms of the Deposit Agreement and the applicable ADR(s), and (b) appoint the Depositary its attorney-in-fact, with full power to delegate, to act on its behalf and to take any and all actions contemplated in the Deposit Agreement and the applicable ADR(s), to adopt any and all procedures necessary to comply with applicable law and to take such action as the Depositary in its sole discretion may deem necessary or appropriate to carry out the purposes of the Deposit Agreement and the applicable ADR(s), the taking of such actions to be the conclusive determinant of the necessity and appropriateness thereof. The manner in which a Beneficial Owner holds ADSs (e.g., in a brokerage account vs. as registered holder) may affect the rights and obligations of, the manner in which, and the extent to which, services are made available to, Beneficial Owners pursuant to the terms of the Deposit Agreement.

The statements made on the face and reverse of this ADR are summaries of certain provisions of the Deposit Agreement and the Articles of Association of the Company (as in effect on the date of the signing of the Deposit Agreement) and are qualified by and subject to the detailed provisions of the Deposit Agreement and the Articles of Association, to which reference is hereby made.

All capitalized terms not defined herein shall have the meanings ascribed thereto in the Deposit Agreement.

The Depositary makes no representation or warranty as to the validity or worth of the Deposited Property. The Depositary has made arrangements for the acceptance of the ADSs into DTC. Each Beneficial Owner of ADSs held through DTC must rely on the procedures of DTC and the DTC Participants to exercise and be entitled to any rights attributable to such ADSs. The Depositary may issue Uncertificated ADSs subject, however, to the terms and conditions of Section 2.13 of the Deposit Agreement.

(2) **Surrender of ADSs and Withdrawal of Deposited Securities.** The Holder of this ADR (and of the ADSs evidenced hereby) shall be entitled to Delivery (at the Custodian's designated office) of the Deposited Securities at the time represented by the ADSs evidenced hereby upon satisfaction of each of the following conditions: (i) the Holder (or a duly-authorized attorney of the Holder) has duly Delivered ADSs to the Depositary at its Principal Office the ADSs evidenced hereby (and, if applicable, this ADR evidencing such ADSs) for the purpose of withdrawal of the Deposited Securities represented hereby, (ii) if applicable and so required by the Depositary, this ADR Delivered to the Depositary for such purpose has been properly endorsed in blank or is accompanied by proper instruments of transfer in blank (including signature guarantees in accordance with standard securities industry practice), (iii) if so required by the Depositary, the Holder of the ADSs has executed and delivered to the Depositary a written order directing the Depositary to cause the Deposited Securities being withdrawn to be Delivered to or upon the written order of the person(s) designated in such order, and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case*, to the terms and conditions of this ADR evidencing the surrendered ADSs, of the Deposit Agreement, of the Company's Articles of Association and of any applicable laws and the rules of CREST, and to any provisions of or governing the Deposited Securities, in each case as in effect at the time thereof.

Upon satisfaction of each of the conditions specified above, the Depositary (i) shall cancel the ADSs Delivered to it (and, if applicable, this ADR(s) evidencing the ADSs so Delivered), (ii) shall direct the Registrar to record the cancellation of the ADSs so Delivered on the books maintained for such purpose, and (iii) shall direct the Custodian to Deliver, or cause the Delivery of, in each case, without unreasonable delay, the Deposited Securities represented by the ADSs so canceled together with any certificate or other document of title for the Deposited Securities, or evidence of the electronic transfer thereof (if available), as the case may be, to or upon the written order of the person(s) designated in the order delivered to the Depositary for such purpose, *subject however, in each case*, to the terms and conditions of the Deposit Agreement, of this ADR evidencing the ADS so canceled, of the Articles of Association of the Company, of any applicable laws and of the rules of CREST, and to the terms and conditions of or governing the Deposited Securities, in each case as in effect at the time thereof.

The Depositary shall not accept for surrender ADSs representing less than one (1) Share. In the case of Delivery to it of ADSs representing a number other than a whole number of Shares, the Depositary shall cause ownership of the appropriate whole number of Shares to be Delivered in accordance with the terms hereof, and shall, at the discretion of the Depositary, either (i) return to the person surrendering such ADSs the number of ADSs representing any remaining fractional Share, or (ii) sell or cause to be sold the fractional Share represented by the ADSs so surrendered and remit the proceeds of such sale (net of (a) applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld as a result of such sale) to the person surrendering the ADSs.

Notwithstanding anything else contained in this ADR or the Deposit Agreement, the Depositary may make delivery at the Principal Office of the Depositary of Deposited Property consisting of (i) any cash dividends or cash distributions, or (ii) any proceeds from the sale of any non-cash distributions, which are at the time held by the Depositary in respect of the Deposited Securities represented by the ADSs surrendered for cancellation and withdrawal. At the request, risk and expense of any Holder so surrendering ADSs represented by this ADR, and for the account of such Holder, the Depositary shall direct the Custodian to forward (to the extent permitted by law) any Deposited Property (other than Deposited Securities) held by the Custodian in respect of such ADSs to the Depositary for delivery at the Principal Office of the Depositary. Such direction shall be given by letter or, at the request, risk and expense of such Holder, by cable, telex or facsimile transmission.

(3) **Transfer, Combination and Split-up of ADRs.** The Registrar shall register the transfer of this ADR (and of the ADSs represented hereby) on the books maintained for such purpose and the Depositary shall (x) cancel this ADR and execute new ADRs evidencing the same aggregate number of ADSs as those evidenced by this ADR canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs, and (z) Deliver such new ADRs to or upon the order of the person entitled thereto, if each of the following conditions has been satisfied: (i) this ADR has been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a transfer thereof, (ii) this surrendered ADR has been properly endorsed or is accompanied by proper instruments of transfer (including signature guarantees in accordance with standard securities industry practice), (iii) this surrendered ADR has been duly stamped (if required by the laws of the State of New York or of the United States), and (iv) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case*, to the terms and conditions of this ADR, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

The Registrar shall register the split-up or combination of this ADR (and of the ADSs represented hereby) on the books maintained for such purpose and the Depositary shall (x) cancel this ADR and execute new ADRs for the number of ADSs requested, but in the aggregate not exceeding the number of ADSs evidenced by this ADR canceled by the Depositary, (y) cause the Registrar to countersign such new ADRs, and (z) Deliver such new ADRs to or upon the order of the Holder thereof, if each of the following conditions has been satisfied: (i) this ADR has been duly Delivered by the Holder (or by a duly authorized attorney of the Holder) to the Depositary at its Principal Office for the purpose of effecting a split-up or combination hereof, and (ii) all applicable fees and charges of, and expenses incurred by, the Depositary and all applicable taxes and governmental charges (as are set forth in Section 5.9 of, and Exhibit B to, the Deposit Agreement) have been paid, *subject, however, in each case*, to the terms and conditions of this ADR, of the Deposit Agreement and of applicable law, in each case as in effect at the time thereof.

(4) **Pre-Conditions to Registration, Transfer, Etc.** As a condition precedent to the execution and Delivery, the registration of issuance, transfer, split-up, combination or surrender, of any ADS, the delivery of any distribution thereon, or the withdrawal of any Deposited Property, the Depositary or the Custodian may require (i) payment from the depositor of Shares or presenter of ADSs or of this ADR of a sum sufficient to reimburse it for any tax or other governmental charge and any stock transfer or registration fee with respect thereto (including any such tax or charge and fee with respect to Shares being deposited or withdrawn) and payment of any applicable fees and charges of the Depositary as provided in Section 5.9 and Exhibit B to the Deposit Agreement and in this ADR, (ii) the production of proof reasonably satisfactory to it as to the identity and genuineness of any signature or any other matter contemplated by Section 3.1 of the Deposit Agreement, and (iii) compliance with (A) any laws or governmental regulations relating to the execution and Delivery of this ADR or ADSs or to the withdrawal of Deposited Securities and (B) such reasonable regulations as the Depositary and the Company may establish consistent with the provisions of this ADR, if applicable, the Deposit Agreement and applicable law.

The issuance of ADSs against deposits of Shares generally or against deposits of particular Shares may be suspended, or the deposit of particular Shares may be refused, or the registration of transfer of ADSs in particular instances may be refused, or the registration of transfer of ADSs generally may be suspended, during any period when the transfer books of the Company, the Depositary, a Registrar or the Share Registrar are closed or if any such action is deemed necessary or advisable by the Depositary or the Company, in good faith, at any time or from time to time because of any requirement of law or regulation, any government or governmental body or commission or any securities exchange on which the ADSs or Shares are listed, or under any provision of the Deposit Agreement or this ADR, if applicable, or under any provision of, or governing, the Deposited Securities, or because of a meeting of shareholders of the Company or for any other reason, subject, in all cases to Section 7.8 of the Deposit Agreement and paragraph (25) of this ADR. Notwithstanding any provision of the Deposit Agreement or this ADR to the contrary, Holders are entitled to surrender outstanding ADSs to withdraw the Deposited Securities associated therewith at any time subject only to (i) temporary delays caused by closing the transfer books of the Depositary or the Company or the deposit of Shares in connection with voting at a shareholders' meeting or the payment of dividends, (ii) the payment of fees, taxes and similar charges, (iii) compliance with any U.S. or foreign laws or governmental regulations relating to the ADSs or to the withdrawal of the Deposited Securities, and (iv) other circumstances specifically contemplated by Instruction I.A.(l) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time).

(5) **Compliance With Information Requests.** Notwithstanding any other provision of the Deposit Agreement or this ADR, each Holder and Beneficial Owner of the ADSs represented hereby agrees to comply with requests from the Company pursuant to applicable law, the rules and requirements of any stock exchange on which the Shares or ADSs are, or will be, registered, traded or listed, or the Articles of Association of the Company, which are made to provide information, *inter alia*, as to the capacity in which such Holder or Beneficial Owner owns ADSs (and the Shares represented by such ADSs, as the case may be) and regarding the identity of any other person(s) interested in such ADSs (and the Shares represented by such ADSs, as the case may be) and the nature of such interest and various other matters, whether or not they are Holders and/or Beneficial Owners at the time of such request.

(6) **Ownership Restrictions.** Notwithstanding any other provision of this ADR or of the Deposit Agreement, the Company may restrict transfers of the Shares where such transfer might result in ownership of Shares exceeding limits imposed by applicable law or the Articles of Association of the Company. The Company may also restrict, in such manner as it deems appropriate, transfers of the ADSs where such transfer may result in the total number of Shares represented by the ADSs owned by a single Holder or Beneficial Owner to exceed any such limits. The Company may, in its sole discretion but subject to applicable law, instruct the Depositary to take action with respect to the ownership interest of any Holder or Beneficial Owner in excess of the limits set forth in the preceding sentence, including but not limited to, the imposition of restrictions on the transfer of ADSs, the removal or limitation of voting rights or the mandatory sale or disposition on behalf of a Holder or Beneficial Owner of the Shares represented by the ADSs held by such Holder or Beneficial Owner in excess of such limitations, if and to the extent such disposition is permitted by applicable law and the Articles of Association of the Company. Nothing herein or in the Deposit Agreement shall be interpreted as obligating the Depositary or the Company to ensure compliance with the ownership restrictions described herein or in Section 3.5 of the Deposit Agreement.

Notwithstanding any provision of this ADR or the Deposit Agreement and without limiting the foregoing, by being a Holder of this ADR (and of the ADSs evidenced hereby), the Holder agrees to provide such information as the Company may request in a disclosure notice (a "Disclosure Notice") given pursuant to the U.K. Companies Act 2006 (as amended from time to time and including any statutory modification or re-enactment thereof, the "Companies Act") or the Articles of Association of the Company. By accepting or holding this ADR, the Holder acknowledges that it understands that failure to comply with a Disclosure Notice may result in the imposition of sanctions against the Holder of the Shares in respect of which the non-complying person is or was, or appears to be or has been, interested as provided in the Companies Act and the Articles of Association which currently include, the withdrawal of the voting rights of such Shares and the imposition of restrictions on the rights to receive dividends on and to transfer such Shares.

(7) **Reporting Obligations and Regulatory Approvals.** Applicable laws and regulations may require holders and beneficial owners of Shares, including the Holders and Beneficial Owners of ADSs, to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. Holders and Beneficial Owners of ADSs are solely responsible for determining and complying with such reporting requirements and obtaining such approvals. Each Holder and each Beneficial Owner hereby agrees to make such determination, file such reports, and obtain such approvals to the extent and in the form required by applicable laws and regulations as in effect from time to time. Neither the Depositary, the Custodian, the Company or any of their respective agents or affiliates shall be required to take any actions whatsoever on behalf of Holders or Beneficial Owners to determine or satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

(8) **Liability for Taxes and Other Charges.** Any tax or other governmental charge payable by the Custodian or by the Depositary with respect to any Deposited Property, ADSs or this ADR shall be payable by the Holders and Beneficial Owners to the Depositary. The Company, the Custodian and/or the Depositary may withhold or deduct from any distributions made in respect of Deposited Property, and may sell for the account of a Holder and/or Beneficial Owner any or all of the Deposited Property and apply such distributions and sale proceeds in payment of, any taxes (including applicable interest and penalties) or charges that are or may be payable by Holders or Beneficial Owners in respect of the ADSs, Deposited Property and this ADR, the Holder and the Beneficial Owner hereof remaining liable for any deficiency. The Custodian may refuse the deposit of Shares and the Depositary may refuse to issue ADSs, to deliver ADRs, register the transfer of ADSs, register the split-up or combination of ADRs and (subject to paragraph (25) of this ADR and Section 7.8 of the Deposit Agreement) the withdrawal of Deposited Property until payment in full of such tax, charge, penalty or interest is received. Every Holder and Beneficial Owner agrees to indemnify the Depositary, the Company, the Custodian, and any of their agents, officers, employees and Affiliates for, and to hold each of them harmless from, any claims with respect to taxes (including applicable interest and penalties thereon) arising from any tax benefit obtained for such Holder and/or Beneficial Owner. The obligations of Holders and Beneficial Owners under this paragraph (8) and Section 3.2 of the Deposit Agreement shall survive any transfer of ADSs, any cancellation of ADSs and withdrawal of Deposited Securities, and the termination of the Deposit Agreement.

(9) **Representations and Warranties on Deposit of Shares.** Each person depositing Shares under the Deposit Agreement shall be deemed thereby to represent and warrant that (i) such Shares and the certificates therefor are duly authorized, validly allotted and issued, fully paid, not subject to any call for payment of further capital and legally obtained by such person, (ii) all preemptive (and similar) rights, if any, with respect to such Shares have been validly waived, disapplied or exercised, (iii) the person making such deposit is duly authorized so to do, (iv) the Shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage or adverse claim, (v) the Shares presented for deposit are not, and the ADSs issuable upon such deposit will not be, Restricted Securities (except as contemplated in Section 2.14 of the Deposit Agreement), (vi) the Shares presented for deposit have not been stripped of any rights or entitlements, and (viii) the deposit of the Shares does not violate any applicable provisions of English law. Such representations and warranties shall survive the deposit and withdrawal of Shares, the issuance and cancellation of ADSs in respect thereof and the transfer of such ADSs. If any such representations or warranties are false in any way, the Company and the Depositary shall be authorized, at the cost and expense of the person depositing Shares, to take any and all actions necessary to correct the consequences thereof.

(10) **Proofs, Certificates and Other Information.** Any person presenting Shares for deposit, any Holder and any Beneficial Owner may be required, and every Holder and Beneficial Owner agrees, from time to time to provide to the Depositary and the Custodian such proof of citizenship or residence, taxpayer status, payment of all applicable taxes or other governmental charges, exchange control approval, legal or beneficial ownership of ADSs and Deposited Property, compliance with applicable laws, the terms of the Deposit Agreement or this ADR evidencing the ADSs and the provisions of, or governing, the Deposited Property, to execute such certifications and to make such representations and warranties, and to provide such other information and documentation (or, in the case of Shares in registered form presented for deposit, such information relating to the registration on the books of the Company or of the Share Registrar) as the Depositary or the Custodian may deem necessary or proper or as the Company may reasonably require by written request to the Depositary consistent with its obligations under the Deposit Agreement and this ADR. The Depositary and the Registrar, as applicable, may and at the reasonable request of the Company shall, to the extent practicable and subject to applicable law, withhold the execution or delivery or registration of transfer of any ADR or ADS or the distribution or sale of any dividend or distribution of rights or of the proceeds thereof or, to the extent not limited by paragraph (25) and Section 7.8 of the Deposit Agreement, the delivery of any Deposited Property until such proof or other information is filed or such certifications are executed, or such representations and warranties are made, or such other documentation or information are provided, in each case to the Depositary's, the Registrar's and the Company's satisfaction.

(11) **ADS Fees and Charges.** The following ADS fees are payable under the terms of the Deposit Agreement:

(i) ADS Issuance Fee: by any person for whom ADSs are issued (*e.g.*, an issuance upon a deposit of Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), excluding issuances as a result of distributions described in paragraph (iv) below, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) issued under the terms of the Deposit Agreement;

(ii) ADS Cancellation Fee: by any person for whom ADSs are being cancelled (*e.g.*, a cancellation of ADSs for Delivery of deposited shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) cancelled;

(iii) Cash Distribution Fee: by any Holder of ADSs to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of cash dividends or other cash distributions (*e.g.*, upon a sale of rights and other entitlements);

(iv) Stock Distribution /Rights Exercise Fee: by any Holder of ADS(s) to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of ADSs pursuant to (a) stock dividends or other free stock distributions, or (b) an exercise of rights to purchase additional ADSs;

(v) Other Distribution Fee: by any Holder of ADS(s) to whom the distribution is made, a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held for the distribution of securities other than ADSs or rights to purchase additional ADSs (*e.g.*, spin-off shares); and

(vi) Depositary Services Fee: by any Holder of ADS(s), a fee not in excess of U.S. $5.00 per 100 ADSs (or fraction thereof) held on the applicable record date(s) established by the Depositary.

The Company, Holders, Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with ADS issuances and cancellations, and persons for whom ADSs are issued or cancelled shall be responsible for the following ADS charges under the terms of the Deposit Agreement:

(a) taxes (including applicable interest and penalties) and other governmental charges;

(b) such registration fees as may from time to time be in effect for the registration of Shares or other Deposited Securities on the share register and applicable to transfers of Shares or other Deposited Securities to or from the name of the Custodian, the Depositary or any nominees upon the making of deposits and withdrawals, respectively;

(c) such cable, telex and facsimile transmission and delivery expenses as are expressly provided in the Deposit Agreement to be at the expense of the person depositing Shares or withdrawing Deposited Property or of the Holders and Beneficial Owners of ADSs;

(d) the expenses and charges incurred by the Depositary in the conversion of foreign currency (including transaction spreads);

(e) such fees and expenses as are incurred by the Depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to Deposited Property, ADSs and ADRs; and

(f) the fees and expenses incurred by the Depositary, the Custodian, or any nominee in connection with the delivery or servicing of Deposited Property.

All ADS fees and charges so payable may be deducted from distributions or must be remitted to the Depositary, or its designee, may, at any time and from time to time, be changed by agreement between the Depositary and Company but, in the case of ADS fees and charges payable by Holders and Beneficial Owners, only in the manner contemplated by paragraph (23) of this ADR and as contemplated in Section 6.1 of the Deposit Agreement. The Depositary shall provide, without charge, a copy of its latest ADS fee schedule to anyone upon request.

ADS fees and charges payable upon (i) the issuance of ADSs and (ii) the cancellation of ADSs will be payable by the person for whom the ADSs are so issued by the Depositary (in the case of ADS issuances) and by the person for whom ADSs are being cancelled by the Depositary (in the case of ADS cancellations). In the case of ADSs issued by the Depositary into DTC or presented to the Depositary via DTC, the ADS issuance and cancellation fees and charges will be payable by the DTC Participant(s) receiving the ADSs from the Depositary or the DTC Participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the Beneficial Owner(s) and will be charged by the DTC Participant(s) to the account(s) of the applicable Beneficial Owner(s) in accordance with the procedures and practices of the DTC Participant(s) as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are payable by Holders as of the applicable ADS Record Date established by the Depositary. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, the applicable Holders as of the ADS Record Date established by the Depositary will be invoiced for the amount of the ADS fees and charges and such ADS fees may be deducted from distributions made to Holders. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC and may be charged to the DTC Participants in accordance with the procedures and practices prescribed by DTC from time to time and the DTC Participants in turn charge the amount of such ADS fees and charges to the Beneficial Owners for whom they hold ADSs.

The Depositary may reimburse the Company for certain expenses incurred by the Company in respect of the ADR program established pursuant to the Deposit Agreement, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as the Company and the Depositary agree from time to time. The Company shall pay to the Depositary such fees and charges, and reimburse the Depositary for such out-of-pocket expenses, as the Depositary and the Company may agree from time to time. Responsibility for payment of such fees, charges and reimbursements may from time to time be changed by agreement between the Company and the Depositary. Unless otherwise agreed, the Depositary shall present its statement for such fees, charges and reimbursements to the Company once every three months. The charges and expenses of the Custodian are for the sole account of the Depositary.

The obligations of Holders and Beneficial Owners to pay ADS fees and charges shall survive the termination of the Deposit Agreement. As to any Depositary, upon the resignation or removal of such Depositary as described in Section 5.4 of the Deposit Agreement, the right to collect ADS fees and charges shall extend for those ADS fees and charges incurred prior to the effectiveness of such resignation or removal.

(12) **Title to ADRs.** Subject to the limitations contained in the Deposit Agreement and in this ADR, it is a condition of this ADR, and every successive Holder of this ADR by accepting or holding the same consents and agrees, that title to this ADR (and to each Certificated ADS evidenced hereby) shall be transferable upon the same terms as a certificated security under the laws of the State of New York, provided that, in the case of Certificated ADSs, this ADR has been properly endorsed or is accompanied by proper instruments of transfer. Notwithstanding any notice to the contrary, the Depositary and the Company may deem and treat the Holder of this ADR (that is, the person in whose name this ADR is registered on the books of the Depositary) as the absolute owner thereof for all purposes. Neither the Depositary nor the Company shall have any obligation nor be subject to any liability under the Deposit Agreement or this ADR to any holder of this ADR or any Beneficial Owner unless, in the case of a holder of ADSs, such holder is the Holder of this ADR registered on the books of the Depositary or, in the case of a Beneficial Owner, such Beneficial Owner, or the Beneficial Owner's representative, is the Holder registered on the books of the Depositary.

(13) **Validity of ADR.** The Holder(s) of this ADR (and the ADSs represented hereby) shall not be entitled to any benefits under the Deposit Agreement or be valid or enforceable for any purpose against the Depositary or the Company unless this ADR has been (i) dated, (ii) signed by the manual or facsimile signature of a duly-authorized signatory of the Depositary, (iii) countersigned by the manual or facsimile signature of a duly-authorized signatory of the Registrar, and (iv) registered in the books maintained by the Registrar for the registration of issuances and transfers of ADRs. An ADR bearing the facsimile signature of a duly-authorized signatory of the Depositary or the Registrar, who at the time of signature was a duly authorized signatory of the Depositary or the Registrar, as the case may be, shall bind the Depositary, notwithstanding the fact that such signatory has ceased to be so authorized prior to the delivery of such ADR by the Depositary.

(14) **Available Information; Reports; Inspection of Transfer Books.** The Company is subject to the periodic reporting requirements of the Exchange Act and, accordingly, is required to file or furnish certain reports with the Commission. These reports can be retrieved from the Commission's website (www.sec.gov) and can be inspected and copied at the public reference facilities maintained by the Commission located (as of the date of the Deposit Agreement) at 100 F Street, N.E., Washington D.C. 20549. The Depositary shall make available for inspection by Holders at its Principal Office, as promptly as practicable after receipt thereof, any reports and communications, including any proxy soliciting materials, received from the Company which are both (a) received by the Depositary, the Custodian, or the nominee of either of them as the holder of the Deposited Property and (b) made generally available to the holders of such Deposited Property by the Company.

The Registrar shall keep books for the registration of ADSs which at all reasonable times shall be open for inspection by the Company and by the Holders of such ADSs, provided that such inspection shall not be, to the Registrar's knowledge, for the purpose of communicating with Holders of such ADSs in the interest of a business or object other than the business of the Company or other than a matter related to the Deposit Agreement or the ADSs.

The Registrar may close the transfer books with respect to the ADSs, at any time or from time to time, when deemed necessary or advisable by it in good faith in connection with the performance of its duties hereunder, or at the reasonable written request of the Company subject, in all cases, to paragraph (25) and Section 7.8 of the Deposit Agreement.

Dated:

CITIBANK, N.A.
Transfer Agent and Registrar

By: _____
Authorized Signatory

CITIBANK, N.A.
as Depositary

By: _____
Authorized Signatory

The address of the Principal Office of the Depositary is 388 Greenwich Street, New York, New York 10013, U.S.A.

[FORM OF REVERSE OF ADR]

SUMMARY OF CERTAIN ADDITIONAL PROVISIONS

OF THE DEPOSIT AGREEMENT

(15) **Dividends and Distributions in Cash, Shares, etc.** (a) ***Cash Distributions***: Whenever the Company intends to make a distribution of a cash dividend or other cash distribution in respect of any Deposited Securities, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable for determining the holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt by the Depositary of a notice from the Company that it intends to make a distribution of a cash dividend or other cash distribution, the Depositary shall establish an ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement. Upon receipt of confirmation of receipt of (x) any cash dividend or other cash distribution on any Deposited Securities, or (y) proceeds from the sale of any Deposited Property held in respect of the ADSs under the terms of the Deposit Agreement, the Depositary will (i) if at the time of receipt thereof any amounts received in a Foreign Currency can, in the judgment of the Depositary (pursuant to Section 4.8 of the Deposit Agreement), be converted on a practicable basis into Dollars transferable to the United States, promptly convert or cause to be converted such cash dividend, distribution or proceeds into Dollars (on the terms described in Section 4.8 of the Deposit Agreement), (ii) if applicable and unless previously established, establish the ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement, and (iii) distribute promptly the amount thus received (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld in connection with the distribution) to the Holders entitled thereto as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date. The Depositary shall distribute only such amount, however, as can be distributed without attributing to any Holder a fraction of one cent, and any balance not so distributed shall be held by the Depositary (without liability for interest thereon) and shall be added to and become part of the next sum received by the Depositary for distribution to Holders of ADSs outstanding at the time of the next distribution. If the Company, the Custodian or the Depositary is required to withhold and does withhold from any cash dividend or other cash distribution in respect of any Deposited Securities, or from any cash proceeds from the sales of Deposited Property, an amount on account of taxes, duties or other governmental charges, the amount distributed to Holders on the ADSs shall be reduced accordingly. Such withheld amounts shall be forwarded by the Company, the Custodian or the Depositary to the relevant governmental authority. Evidence of payment thereof by the Company shall be forwarded by the Company to the Depositary upon request. The Depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable Holders and Beneficial Owners of ADSs until the distribution can be effected or the funds that the Depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.1 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.1 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(b) ***Share Distributions***: Whenever the Company intends to make a distribution that consists of a dividend in, or free distribution of, Shares, the Company shall give notice thereof to the Depositary at least twenty (20) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution, specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution. Upon the timely receipt by the Depositary of a notice from the Company that it intends to make a distribution that consists of a dividend in, or free distribution of Shares, the Depositary shall establish the ADS Record Date upon the terms described in Section 4.9 of the Deposit Agreement. Upon receipt of confirmation from the Custodian of the receipt of the Shares so distributed by the Company, the Depositary shall either (i) subject to Section 5.9 of the Deposit Agreement, distribute to the Holders as of the ADS Record Date in proportion to the number of ADSs held as of the ADS Record Date, additional ADSs, which represent in the aggregate the number of Shares received as such dividend, or free distribution, subject to the other terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary and (b) applicable taxes required to be withheld), or (ii) if additional ADSs are not so distributed, take all actions necessary so that each ADS issued and outstanding after the ADS Record Date shall, to the extent permissible by law, thenceforth also represent rights and interests in the additional integral number of Shares distributed upon the Deposited Securities represented thereby (net of (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes). In lieu of delivering fractional ADSs, the Depositary shall sell the number of Shares or ADSs, as the case may be, represented by the aggregate of such fractions and distribute the net proceeds upon the terms described in Section 4.1 of the Deposit Agreement.

In the event that the Depositary determines that any distribution in property (including Shares) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, or, if the Company in the fulfillment of its obligations under Section 5.7 of the Deposit Agreement, has furnished an opinion of U.S. counsel determining that Shares must be registered under the Securities Act or other laws in order to be distributed to Holders (and no such registration statement has been declared effective), the Depositary may dispose of all or a portion of such property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable, and the Depositary shall distribute the net proceeds of any such sale (after deduction of (a) applicable taxes required to be withheld and (b) fees and charges of, and the expenses incurred by, the Depositary) to Holders entitled thereto upon the terms of Section 4.1 of the Deposit Agreement. The Depositary shall hold and/or distribute any unsold balance of such property in accordance with the provisions of the Deposit Agreement. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.2 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.2 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(c) ***Elective Distributions in Cash or Shares***: Whenever the Company intends to make a distribution payable at the election of the holders of Deposited Securities in cash or in additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such elective distribution and whether or not it wishes such elective distribution to be made available to Holders of ADSs. Upon the timely receipt of a notice indicating that the Company wishes an elective distribution in cash or Shares to be made available to Holders of ADSs upon the terms described in the Deposit Agreement, the Company and the Depositary shall determine in accordance with the Deposit Agreement whether such distribution is lawful and reasonably practicable. The Depositary shall make such elective distribution available to Holders only if (i) the Company shall have timely requested that the elective distribution be made available to Holders, (ii) the Depositary shall have determined that such distribution is reasonably practicable and (iii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7 of the Deposit Agreement. If the above conditions are satisfied, the Depositary shall, subject to the terms and conditions of the Deposit Agreement, establish the ADS Record Date according to paragraph (16) and Section 4.9 of the Deposit Agreement and establish procedures to enable the Holder hereof to elect to receive the proposed distribution in cash or in additional ADSs. If a Holder elects to receive the distribution in cash, the distribution shall be made as in the case of a distribution in cash. If the Holder hereof elects to receive the distribution in additional ADSs, the distribution shall be made as in the case of a distribution in Shares upon the terms described in the Deposit Agreement. If such elective distribution is not reasonably practicable or if the Depositary did not receive satisfactory documentation set forth in the Deposit Agreement, the Depositary shall establish an ADS Record Date upon the terms of Section 4.9 of the Deposit Agreement and, to the extent permitted by law, distribute to Holders, on the basis of the same determination as is made in England and Wales in respect of the Shares for which no election is made, either (x) cash upon the terms described in Section 4.1 of the Deposit Agreement or (y) additional ADSs representing such additional Shares upon the terms described in Section 4.2 of the Deposit Agreement. Nothing herein or in the Deposit Agreement shall obligate the Depositary to make available to the Holder hereof a method to receive the elective distribution in Shares (rather than ADSs). There can be no assurance that the Holder hereof will be given the opportunity to receive elective distributions on the same terms and conditions as the holders of Shares. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed distribution provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.3 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.3 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(d) ***Distribution of Rights to Purchase Additional ADSs***: Whenever the Company intends to distribute to the holders of the Deposited Securities rights to subscribe for additional Shares, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the proposed distribution specifying, *inter alia*, the record date applicable to holders of Deposited Securities entitled to receive such distribution and whether or not it wishes such rights to be made available to Holders of ADSs. Upon the timely receipt by the Depositary of a notice indicating that the Company wishes rights to subscribe for additional Shares to be made available to Holders of ADSs, the Depositary upon consultation with the Company, shall determine, whether it is lawful and reasonably practicable to make such rights available to the Holders. The Depositary shall make such rights available to any Holders only if (i) the Company shall have timely requested that such rights be made available to Holders, (ii) the Depositary shall have received satisfactory documentation within the terms of Section 5.7 of the Deposit Agreement, and (iii) the Depositary shall have determined that such distribution of rights is reasonably practicable. In the event any of the conditions set forth above are not satisfied or if the Company requests that the rights not be made available to Holders of ADSs, the Depositary shall proceed with the sale of the rights as described below. In the event all conditions set forth above are satisfied, the Depositary shall establish the ADS Record Date (upon the terms described in Section 4.9 of the Deposit Agreement) and establish procedures to (x) distribute rights to purchase additional ADSs (by means of warrants or otherwise), (y) enable the Holders to exercise such rights (upon payment of the subscription price and of the applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes), and (z) deliver ADSs upon the valid exercise of such rights. Nothing herein or in the Deposit Agreement shall obligate the Depositary to make available to the Holders a method to exercise rights to subscribe for Shares (rather than ADSs). If (i) the Company does not timely request the Depositary to make the rights available to Holders or requests that the rights not be made available to Holders, (ii) the Depositary fails to receive satisfactory documentation within the terms of Section 5,7 of the Deposit Agreement or determines it is not reasonably practicable to make the rights available to Holders, or (iii) any rights made available are not exercised and appear to be about to lapse, the Depositary shall determine whether it is lawful and reasonably practicable to sell such rights, in a riskless principal capacity, at such place and upon such terms (including public and private sale) as it may deem practicable. The Depositary shall, upon such sale, convert and distribute proceeds of such sale (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) upon the terms hereof and of Section 4.1 of the Deposit Agreement. If the Depositary is unable to make any rights available to Holders upon the terms described in Section 4.4(a) of the Deposit Agreement or to arrange for the sale of the rights upon the terms described in Section 4.4(b) of the Deposit Agreement, the Depositary shall allow such rights to lapse. The Depositary shall not be liable for (i) any failure to accurately determine whether it may be lawful or practicable to make such rights available to Holders in general or any Holders in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale or exercise, or (iii) the content of any materials forwarded to the Holders on behalf of the Company in connection with the rights distribution.

Notwithstanding anything herein or in Section 4.4 of the Deposit Agreement to the contrary, if registration (under the Securities Act or any other applicable law) of the rights or the securities to which any rights relate may be required in order for the Company to offer such rights or such securities to Holders and to sell the securities represented by such rights, the Depositary will not distribute such rights to the Holders (i) unless and until a registration statement under the Securities Act (or other applicable law) covering such offering is in effect or (ii) unless the Company furnishes the Depositary opinion(s) of counsel for the Company in the United States and counsel to the Company in any other applicable country in which rights would be distributed, in each case satisfactory to the Depositary, to the effect that the offering and sale of such securities to Holders and Beneficial Owners are exempt from, or do not require registration under, the provisions of the Securities Act or any other applicable laws. In the event that the Company, the Depositary or the Custodian shall be required to withhold and does withhold from any distribution of Deposited Property (including rights) an amount on account of taxes or other governmental charges, the amount distributed to the Holders of ADSs shall be reduced accordingly. In the event that the Depositary determines that any distribution of Deposited Property (including Shares and rights to subscribe therefor) is subject to any tax or other governmental charges which the Depositary is obligated to withhold, the Depositary may dispose of all or a portion of such Deposited Property (including Shares and rights to subscribe therefor) in such amounts and in such manner, including by public or private sale, as the Depositary deems necessary and practicable to pay any such taxes or charges.

There can be no assurance that Holders generally, or any Holder in particular, will be given the opportunity to receive or exercise rights on the same terms and conditions as the holders of Shares or be able to exercise such rights. Nothing herein or in the Deposit Agreement shall obligate the Company to file any registration statement in respect of any rights or Shares or other securities to be acquired upon the exercise of such rights.

(e) ***Distributions other than Cash, Shares or Rights to Purchase Shares***: Whenever the Company intends to distribute to the holders of Deposited Securities property other than cash, Shares or rights to purchase additional Shares, the Company shall give timely notice thereof to the Depositary and shall indicate whether or not it wishes such distribution to be made to Holders of ADSs. Upon receipt of a notice indicating that the Company wishes property other than cash, Shares or rights to purchase additional Shares to be made to Holders of ADSs, the Depositary shall consult with the Company, and the Company shall assist the Depositary, to determine whether such distribution to Holders is lawful and reasonably practicable. The Depositary shall not make such distribution unless (i) the Company shall have requested the Depositary to make such distribution to Holders, (ii) the Depositary shall have received the documentation contemplated in the Deposit Agreement, and (iii) the Depositary shall have determined that such distribution is reasonably practicable. Upon satisfaction of such conditions, the Depositary shall distribute the property so received to the Holders of record, as of the ADS Record Date, in proportion to the number of ADSs held by them respectively and in such manner as the Depositary may deem practicable for accomplishing such distribution (i) upon receipt of payment or net of the applicable fees and charges of, and expenses incurred by, the Depositary, and (ii) net of any applicable taxes required to be withheld. The Depositary may dispose of all or a portion of the property so distributed and deposited, in such amounts and in such manner (including public or private sale) as the Depositary may deem practicable or necessary to satisfy any taxes (including applicable interest and penalties) or other governmental charges applicable to the distribution.

If the conditions above are not satisfied, the Depositary shall sell or cause such property to be sold in a public or private sale, at such place or places and upon such terms as it may deem practicable and shall (i) cause the proceeds of such sale, if any, to be converted into Dollars and (ii) distribute the proceeds of such conversion received by the Depositary (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) to the Holders as of the ADS Record Date upon the terms hereof and of the Deposit Agreement. If the Depositary is unable to sell such property, the Depositary may dispose of such property for the account of the Holders in any way it deems reasonably practicable under the circumstances.

Neither the Depositary nor the Company shall be liable for (i) any failure to accurately determine whether it is lawful or practicable to make the property described in Section 4.5 of the Deposit Agreement available to Holders in general or any Holders in particular, nor (ii) any loss incurred in connection with the sale or disposal of such property.

(f) ***Distributions with Respect to Deposited Securities in Bearer Form***: Subject to the terms of this paragraph (15) and Article IV of the Deposit Agreement, distributions in respect of Deposited Securities that are held by the Depositary or the Custodian in bearer form shall be made to the Depositary for the account of the respective Holders of ADS(s) with respect to which any such distribution is made upon due presentation by the Depositary or the Custodian to the Company of any relevant coupons, talons, or certificates. The Company shall promptly notify the Depositary of such distributions. The Depositary or the Custodian shall promptly present such coupons, talons or certificates, as the case may be, in connection with any such distribution.

(16) **Redemption.** If the Company intends to exercise any right of redemption in respect of any of the Deposited Securities, the Company shall give notice thereof to the Depositary at least forty-five (45) days (or such other number of days as mutually agreed to in writing by the Depositary and the Company) prior to the intended date of redemption which notice shall set forth the particulars of the proposed redemption. Upon timely receipt of notice from the Company that it intends to exercise its right of redemption in respect of any of the Deposited Securities, and satisfactory documentation, and, after consultation between the Depositary and the Custodian, upon determining that such proposed redemption is practicable, the Depositary shall provide to each Holder a notice setting forth the Company's intention to exercise the redemption rights and any other particulars set forth in the Company's notice to the Depositary. The Depositary shall instruct the Custodian to present to the Company the Deposited Securities in respect of which redemption rights are being exercised against payment of the applicable redemption price. Upon receipt of confirmation from the Custodian that the redemption has taken place and that funds representing the redemption price have been received, the Depositary shall convert, transfer, and distribute the proceeds (net of applicable (a) fees and charges of, and the expenses incurred by, the Depositary, and (b) taxes), retire ADSs and cancel ADRs, if applicable, upon delivery of such ADSs by Holders thereof and the terms set forth in Sections 4.1 and 6.2 of the Deposit Agreement. If less than all outstanding Deposited Securities are redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as may be determined by the Depositary after consultation with the Company. The redemption price per ADS shall be the dollar equivalent of the per share amount received by the Depositary (adjusted to reflect the ADS(s)-to-Share(s) ratio) upon the redemption of the Deposited Securities represented by ADSs (subject to the terms of Section 4.8 of the Deposit Agreement and the applicable fees and charges of, and expenses incurred by, the

Depositary, and applicable taxes) multiplied by the number of Deposited Securities represented by each ADS redeemed. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to give the Depositary timely notice of the proposed redemption provided for above, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.7 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.7 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

(17) **Fixing of ADS Record Date.** Whenever (a) the Depositary shall receive notice of the fixing of a record date by the Company for the determination of holders of Deposited Securities entitled to receive any distribution (whether in cash, Shares, rights or other distribution), (b) for any reason the Depositary causes a change in the number of Shares that are represented by each ADS, (c) the Depositary shall receive notice of any meeting of, or solicitation of consents or proxies of, holders of Shares or other Deposited Securities, or (d) the Depositary shall find it necessary or convenient in connection with the giving of any notice, solicitation of any consent or any other matter, the Depositary shall fix a record date (the "ADS Record Date") for the determination of the Holders of ADS(s) who shall be entitled to receive such distribution, to give instructions for the exercise of voting rights at any such meeting, to give or withhold such consent, to receive such notice or solicitation or to otherwise take action, or to exercise the rights of Holders with respect to such changed number of Shares represented by each ADS. The Depositary shall make reasonable efforts to establish the ADS Record Date as closely as practicable to the applicable record date for the Deposited Securities (if any) set by the Company in England and Wales and shall not announce the establishment of any ADS Record Date prior to the relevant corporate actions having been made public by the Company (if such corporate action affects the Deposited Securities). Subject to applicable law, the terms and conditions of this ADR, Sections 4.1 through 4.8 of the Deposit Agreement and the other terms and conditions of the Deposit Agreement, only the Holders of ADSs at the close of business in New York on such ADS Record Date shall be entitled to receive such distribution, to give such voting instructions, to receive such notice or solicitation, or otherwise take action.

(18) **Voting of Deposited Securities.** As soon as practicable after receipt of notice of any meeting at which the holders of Deposited Securities are entitled to vote, or of solicitation of consents or proxies from holders of Deposited Securities, the Depositary shall fix the ADS Record Date in respect of such meeting or solicitation of consent or proxy in accordance with Section 4.9 of the Deposit Agreement. The Depositary shall, if requested by the Company in writing in a timely manner (the Depositary having no obligation to take any further action if the request shall not have been received by the Depositary at least thirty (30) days prior to the date of such vote or meeting), at the Company's expense and provided no U.S. legal prohibitions exist, distribute as soon as practicable after receipt thereof to Holders as of the ADS Record Date: (a) such notice of meeting or solicitation of consent or proxy, (b) a statement that the Holders at the close of business on the ADS Record Date will be entitled, subject to any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of or governing the Deposited Securities (which provisions, if any, shall be summarized in pertinent part by the Company), to instruct the Depositary as to the exercise of the voting rights, if any,

pertaining to the Deposited Securities represented by such Holder's ADSs, and (c) a brief statement as to the manner and timing (such timing to be determined after consultation with the Company) in which such voting instructions may be given to the Depositary or in which voting instructions may be deemed to have been given in accordance with Section 4.10 of the Deposit Agreement if no instructions are received prior to the deadline set for such purposes to the Depositary to give a discretionary proxy to a person designated by the Company. Notwithstanding anything contained in the Deposit Agreement to the contrary, in the event the Company fails to timely request that the Depositary distribute the information as provided for in Section 4.10 of the Deposit Agreement, the Depositary agrees to use commercially reasonable efforts to perform the actions contemplated in Section 4.10 of the Deposit Agreement, and the Company, the Holders and the Beneficial Owners acknowledge that the Depositary shall have no liability for the Depositary's failure to perform the actions contemplated in Section 4.10 of the Deposit Agreement where such notice has not been so timely given, other than its failure to use commercially reasonable efforts, as provided herein.

Notwithstanding anything contained in the Deposit Agreement or this ADR, with the Company's prior written consent, the Depositary may, to the extent not prohibited by law or regulations, or by the requirements of any stock exchange on which the ADSs may be listed, in lieu of distribution of the materials provided to the Depositary in connection with any meeting of, or solicitation of consents or proxies from, holders of Deposited Securities, distribute to the Holders a notice that provides Holders with, or otherwise publicize to Holders, instructions on how to retrieve such materials or receive such materials upon request (*e.g.*, by reference to a website containing the materials for retrieval or a contact for requesting copies of the materials).

The Depositary has been advised by the Company that the Articles of Association (as in effect on the date of the Deposit Agreement), provide that voting at any meeting of shareholders is by show of hands unless a poll is demanded. The Depositary will not join in demanding a poll, whether or not requested to do so by Holders of ADSs. Under the Articles of Association (as in effect on the date of the Deposit Agreement), a poll may be demanded by (i) the chairman of the general meeting; (ii) by at least two members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting; (iii) by any member of members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, for the time being entitled to vote at the meeting representing at least one-tenth of the total voting rights of all the members having the right to vote at the meeting and/or one tenth of the aggregate sum of the total sum paid up on all shares of the Company; or (iv) by any member or members of the Company present in person (or by proxy) or in the case of a member being a corporation by its duly authorized representative or by proxy and, in each case, holding shares conferring a right to vote at the meeting, being shares on which an aggregate sum has been paid up equal to at least one-tenth of the total sum paid up on all the shares conferring that right.

Voting instructions may be given only in respect of a number of ADSs representing an integral number of Deposited Securities. Upon the timely receipt from a Holder of ADSs as of the ADS Record Date of voting instructions in the manner specified by the Depositary, the Depositary shall endeavor, insofar as practicable and permitted under any applicable law, the provisions of the Deposit Agreement, the Articles of Association of the Company and the provisions of the Deposited Securities, to vote, or cause the Custodian to vote, the Deposited Securities (in person or by proxy) represented by such Holder's ADSs as follows: (i) in the event voting takes place at a shareholders' meeting by show of hands, the Depositary will instruct the Custodian to vote all Deposited Securities in accordance with the voting instructions received from a majority of Holders of ADSs who provided voting instructions and (ii) in the event voting takes place at a shareholders' meeting by poll, the Depositary will instruct the Custodian to vote the Deposited Securities in accordance with the voting instructions received from the Holders of ADSs. If the Depositary does not receive voting instructions from a Holder as of the ADS Record Date on or before the date established by the Depositary for such purpose, such Holder shall be deemed, and the Depositary shall deem such Holder, to have instructed the Depositary to give a discretionary proxy to a person designated by the Company to vote the Deposited Securities; provided, however, that no such discretionary proxy shall be given by the Depositary with respect to any matter to be voted upon as to which the Company informs the Depositary that (a) the Company does not wish such proxy to be given, (b) substantial opposition exists, or (c) the rights of holders of Deposited Securities may be adversely affected.

Deposited Securities represented by ADSs for which no timely voting instructions are received by the Depositary from the Holder shall not be voted (except as contemplated herein and in Section 4.10 of the Deposit Agreement). Neither the Depositary nor the Custodian shall under any circumstances exercise any discretion as to voting and neither the Depositary nor the Custodian shall vote, attempt to exercise the right to vote, or in any way make use of, for purposes of establishing a quorum or otherwise, the Deposited Securities represented by ADSs, except pursuant to and in accordance with the voting instructions timely received from Holders or as otherwise contemplated herein or in the Deposit Agreement. If the Depositary timely receives voting instructions from a Holder which fail to specify the manner in which the Depositary is to vote the Deposited Securities represented by such Holder's ADSs, the Depositary will deem such Holder (unless otherwise specified in the notice distributed to Holders) to have instructed the Depositary to vote in favor of the items set forth in such voting instructions.

Notwithstanding anything else contained in this ADR or the Deposit Agreement, the Depositary shall, if so requested in writing by the Company, represent all Deposited Securities (whether or not voting instructions have been received in respect of such Deposited Securities from Holders as of the ADS Record Date) for the sole purpose of establishing quorum at a meeting of shareholders.

Notwithstanding anything else contained in the Deposit Agreement or this ADR, the Depositary shall not have any obligation to take any action with respect to any meeting, or solicitation of consents or proxies, of holders of Deposited Securities if the taking of such action would violate U.S. or English laws. The Company agrees to take any and all actions reasonably necessary and as permitted by the laws of England and Wales to enable Holders and Beneficial Owners to exercise the voting rights accruing to the Deposited Securities and to deliver to the Depositary an opinion of U.S. counsel addressing any actions requested to be taken if so reasonably requested by the Depositary.

There can be no assurance that Holders generally or any Holder in particular will receive the notice described above with sufficient time to enable the Holder to return voting instructions to the Depositary in a timely manner.

(19) **Changes Affecting Deposited Securities.** Upon any change in nominal or par value, split-up, cancellation, consolidation or any other reclassification of Deposited Securities, or upon any recapitalization, reorganization, merger, consolidation or sale of assets affecting the Company or to which it is a party, any property which shall be received by the Depositary or the Custodian in exchange for, or in conversion of, or replacement of, or otherwise in respect of, such Deposited Securities shall, to the extent permitted by law, be treated as new Deposited Property under the Deposit Agreement, and this ADR shall, subject to the provisions of the Deposit Agreement, this ADR evidencing such ADSs and applicable law, represent the right to receive such additional or replacement Deposited Property. In giving effect to such change, split-up, cancellation, consolidation or other reclassification of Deposited Securities, recapitalization, reorganization, merger, consolidation or sale of assets, the Depositary may, with the Company's approval, and shall, if the Company shall so request, subject to the terms of the Deposit Agreement (including, without limitation, (a) the applicable fees and charges of, and expenses incurred by, the Depositary, and (b) applicable taxes) and receipt of an opinion of counsel to the Company satisfactory to the Depositary that such actions are not in violation of any applicable laws or regulations, (i) issue and deliver additional ADSs as in the case of a stock dividend on the Shares, (ii) amend the Deposit Agreement and the applicable ADRs, (iii) amend the applicable Registration Statement(s) on Form F-6 as filed with the Commission in respect of the ADSs, (iv) call for the surrender of outstanding ADRs to be exchanged for new ADRs, and (v) take such other actions as are appropriate to reflect the transaction with respect to the ADSs. Notwithstanding the foregoing, in the event that any Deposited Property so received may not be lawfully distributed to some or all Holders, the Depositary may, with the Company's approval, and shall, if the Company requests, subject to receipt of an opinion of Company's counsel satisfactory to the Depositary that such action is not in violation of any applicable laws or regulations, sell such Deposited Property at public or private sale, at such place or places and upon such terms as it may deem proper and may allocate the net proceeds of such sales (net of applicable (a) fees and charges of, and expenses incurred by, the Depositary and (b) taxes) for the account of the Holders otherwise entitled to such Deposited Property upon an averaged or other practicable basis without regard to any distinctions among such Holders and distribute the net proceeds so allocated to the extent practicable as in the case of a distribution received in cash pursuant to Section 4.1 of the Deposit Agreement. The Depositary shall not be responsible for (i) any failure to determine that it may be lawful or practicable to make such Deposited Property available to Holders in general or to any Holder in particular, (ii) any foreign exchange exposure or loss incurred in connection with such sale, or (iii) any liability to the purchaser of such Deposited Property.

(20) **Exoneration.** Notwithstanding anything contained in the Deposit Agreement or any ADR, neither the Depositary nor the Company shall be obligated to do or perform any act which is inconsistent with the provisions of the Deposit Agreement or incur any liability (to the extent not limited by paragraph (25) hereof) (i) if the Depositary, the Custodian, the Company or their respective agents shall be prevented or forbidden from, or delayed in, doing or performing any act or thing required or contemplated by the terms of the Deposit Agreement and this ADR, by reason of any provision of any present or future law or regulation of the United States, England and Wales or any other country, or of any other governmental authority or regulatory authority or stock exchange, or on account of potential criminal or civil penalties or restraint, or by reason of any provision, present or future, of the Articles of Association of the Company or any provision of or governing any Deposited Securities, or by reason of any act of God or war or other circumstances beyond its control (including, without limitation, nationalization, expropriation, currency restrictions, work stoppage, strikes, civil unrest, acts of terrorism, revolutions, rebellions, explosions and computer failure), (ii) by reason of any exercise of, or failure to exercise, any discretion provided for in the Deposit Agreement or in the Articles of Association of the Company or provisions of or governing Deposited Securities, (iii) for any action or inaction in reliance upon the advice of or information from legal counsel, accountants, any person presenting Shares for deposit, any Holder, any Beneficial Owner or authorized representative thereof, or any other person believed by it in good faith to be competent to give such advice or information, (iv) for the inability by a Holder or Beneficial Owner to benefit from any distribution, offering, right or other benefit which is made available to holders of Deposited Securities but is not, under the terms of the Deposit Agreement, made available to Holders of ADSs, (v) for any action or inaction of any clearing or settlement system (and any participant thereof) for the Deposited Property or the ADSs, or (vi) for any consequential or punitive damages (including lost profits) for any breach of the terms of the Deposit Agreement. The Depositary, its controlling persons, its agents, any Custodian and the Company, its controlling persons and its agents may rely and shall be protected in acting upon any written notice, request or other document believed by it to be genuine and to have been signed or presented by the proper party or parties.

(21) **Standard of Care.** The Company and the Depositary assume no obligation and shall not be subject to any liability under the Deposit Agreement or this ADR to any Holder(s) or Beneficial Owner(s), except that the Company and the Depositary agree to perform their respective obligations specifically set forth in the Deposit Agreement or this ADR without negligence or bad faith. Without limitation of the foregoing, neither the Depositary, nor the Company, nor any of their respective controlling persons, or agents, shall be under any obligation to appear in, prosecute or defend any action, suit or other proceeding in respect of any Deposited Property or in respect of the ADSs, which in its opinion may involve it in expense or liability, unless indemnity satisfactory to it against all expense (including fees and disbursements of counsel) and liability be furnished as often as may be required (and no Custodian shall be under any obligation whatsoever with respect to such proceedings, the responsibility of the Custodian being solely to the Depositary).

The Depositary and its agents shall not be liable for any failure to carry out any instructions to vote any of the Deposited Securities, or for the manner in which any vote is cast or the effect of any vote, provided that any such action or omission is in good faith and without negligence and in accordance with the terms of the Deposit Agreement. The Depositary shall not incur any liability for any failure to accurately determine that any distribution or action may be lawful or reasonably practicable, for the content of any information submitted to it by the Company for distribution to the Holders or for any inaccuracy of any translation thereof, for any investment risk associated with acquiring an interest in the Deposited Property, for the validity or worth of the Deposited Property, for the value of any Deposited Property or any distribution thereon, for any interest on Deposited Property, for any tax consequences that may result from the ownership of ADSs, Shares or other Deposited Property, for the credit-worthiness of any third party, for allowing any rights to lapse upon the terms of the Deposit Agreement, for the failure or timeliness of any notice from the Company, or for any action of or failure to act by, or any information provided or not provided by, DTC or any DTC Participant.

The Depositary shall not be liable for any acts or omissions made by a successor depositary whether in connection with a previous act or omission of the Depositary or in connection with any matter arising wholly after the removal or resignation of the Depositary, provided that in connection with the issue out of which such potential liability arises the Depositary performed its obligations without negligence or bad faith while it acted as Depositary for the Company.

(22) **Resignation and Removal of the Depositary; Appointment of Successor Depositary.** The Depositary may at any time resign as Depositary under the Deposit Agreement by written notice of resignation delivered to the Company, such resignation to be effective on the earlier of (i) the 90th day after delivery thereof to the Company (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2 of the Deposit Agreement), or (ii) the appointment by the Company of a successor depositary and its acceptance of such appointment as provided in the Deposit Agreement. The Depositary may at any time be removed by the Company by written notice of such removal, which removal shall be effective on the later of (i) the 90th day after delivery thereof to the Depositary (whereupon the Depositary shall be entitled to take the actions contemplated in Section 6.2 of the Deposit Agreement), or (ii) upon the appointment by the Company of a successor depositary and its acceptance of such appointment as provided in the Deposit Agreement. In case at any time the Depositary acting hereunder or under the Deposit Agreement shall resign or be removed, the Company shall use its best efforts to appoint a successor depositary, which shall be a bank or trust company having an office in the Borough of Manhattan, the City of New York. Every successor depositary shall be required by the Company to execute and deliver to its predecessor and to the Company an instrument in writing accepting its appointment hereunder, and thereupon such successor depositary, without any further act or deed (except as required by applicable law), shall become fully vested with all the rights, powers, duties and obligations of its predecessor (other than as contemplated in Sections 5.8 and 5.9 of the Deposit Agreement). The predecessor depositary, upon payment of all sums due it and on the written request of the Company shall (i) execute and deliver an instrument transferring to such successor all rights and powers of such predecessor hereunder (other than as contemplated in Sections 5.8 and 5.9 of the Deposit Agreement), (ii) duly assign, transfer and deliver all of the Depositary's right, title and interest to the Deposited Property to such successor, and (iii) deliver to such successor a list of the Holders of all outstanding ADSs and such other information relating to ADSs and Holders thereof as the successor may reasonably request. Any such successor depositary shall promptly provide notice of its appointment to such Holders. Any entity into or with which the Depositary may be merged or consolidated shall be the successor of the Depositary without the execution or filing of any document or any further act.

(23) **Amendment/Supplement.** Subject to the terms and conditions of this paragraph 23, and Section 6.1 of the Deposit Agreement and applicable law, this ADR and any provisions of the Deposit Agreement may at any time and from time to time be amended or supplemented by written agreement between the Company and the Depositary in any respect which they may deem necessary or desirable without the prior written consent of the Holders or Beneficial Owners. Any amendment or supplement which shall impose or increase any fees or charges (other than charges in connection with foreign exchange control regulations, and taxes and other governmental charges, delivery and other such expenses), or which shall otherwise materially prejudice any substantial existing right of Holders or Beneficial Owners, shall not, however, become effective as to outstanding ADSs until the expiration of thirty (30) days after notice of such amendment or supplement shall have been given to the Holders of outstanding ADSs. Notice of any amendment to the Deposit Agreement or any ADR shall not need to describe in detail the specific amendments effectuated thereby, and failure to describe the specific amendments in any such notice shall not render such notice invalid, provided, however, that, in each such case, the notice given to the Holders identifies a means for Holders and Beneficial Owners to retrieve or receive the text of such amendment (*e.g.*, upon retrieval from the Commission's, the Depositary's or the Company's website or upon request from the Depositary). The parties hereto agree that any amendments or supplements which (i) are reasonably necessary (as agreed by the Company and the Depositary) in order for (a) the ADSs to be registered on Form F-6 under the Securities Act or (b) the ADSs to be settled solely in electronic book-entry form and (ii) do not in either such case impose or increase any fees or charges to be borne by Holders, shall be deemed not to materially prejudice any substantial rights of Holders or Beneficial Owners. Every Holder and Beneficial Owner at the time any amendment or supplement so becomes effective shall be deemed, by continuing to hold such ADSs, to consent and agree to such amendment or supplement and to be bound by the Deposit Agreement and this ADR, if applicable, as amended or supplemented thereby. In no event shall any amendment or supplement impair the right of the Holder to surrender such ADS and receive therefor the Deposited Securities represented thereby, except in order to comply with mandatory provisions of applicable law. Notwithstanding the foregoing, if any governmental body should adopt new laws, rules or regulations which would require an amendment of, or supplement to, the Deposit Agreement to ensure compliance therewith, the Company and the Depositary may amend or supplement the Deposit Agreement and this ADR at any time in accordance with such changed laws, rules or regulations. Such amendment or supplement to the Deposit Agreement and this ADR in such circumstances may become effective before a notice of such amendment or supplement is given to Holders or within any other period of time as required for compliance with such laws, rules or regulations.

(24) **Termination.** The Depositary shall, at any time at the written direction of the Company, terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. If ninety (90) days shall have expired after (i) the Depositary shall have delivered to the Company a written notice of its election to resign, or (ii) the Company shall have delivered to the Depositary a written notice of the removal of the Depositary, and, in either case, a successor depositary shall not have been appointed and accepted its appointment as provided in Section 5.4 of the Deposit Agreement, the Depositary may terminate the Deposit Agreement by distributing notice of such termination to the Holders of all ADSs then outstanding at least thirty (30) days prior to the date fixed in such notice for such termination. The date so fixed for

termination of the Deposit Agreement in any termination notice so distributed by the Depositary to the Holders of ADSs is referred to as the "Termination Date". Until the Termination Date, the Depositary shall continue to perform all of its obligations under the Deposit Agreement, and the Holders and Beneficial Owners will be entitled to all of their rights under the Deposit Agreement. If any ADSs shall remain outstanding after the Termination Date, the Registrar and the Depositary shall not, after the Termination Date, have any obligation to perform any further acts under the Deposit Agreement, except that the Depositary shall, subject, in each case, to the terms and conditions of the Deposit Agreement, continue to (i) collect dividends and other distributions pertaining to Deposited Securities, (ii) sell Deposited Property received in respect of Deposited Securities, (iii) deliver Deposited Securities, together with any dividends or other distributions received with respect thereto and the net proceeds of the sale of any other Deposited Property, in exchange for ADSs surrendered to the Depositary (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (iv) take such actions as may be required under applicable law in connection with its role as Depositary under the Deposit Agreement. At any time after the Termination Date, the Depositary may sell the Deposited Property then held under the Deposit Agreement and shall after such sale hold un-invested the net proceeds of such sale, together with any other cash then held by it under the Deposit Agreement, in an un-segregated account and without liability for interest, for the pro rata benefit of the Holders whose ADSs have not theretofore been surrendered. After making such sale, the Depositary shall be discharged from all obligations under the Deposit Agreement except (i) to account for such net proceeds and other cash (after deducting, or charging, as the case may be, in each case, the fees and charges of, and expenses incurred by, the Depositary, and all applicable taxes or governmental charges for the account of the Holders and Beneficial Owners, in each case upon the terms set forth in Section 5.9 of the Deposit Agreement), and (ii) as may be required at law in connection with the termination of the Deposit Agreement. After the Termination Date, the Company shall be discharged from all obligations under the Deposit Agreement, except for its obligations to the Depositary under Sections 5.8, 5.9 and 7.6 of the Deposit Agreement. The obligations under the terms of the Deposit Agreement of Holders and Beneficial Owners of ADSs outstanding as of the Termination Date shall survive the Termination Date and shall be discharged only when the applicable ADSs are presented by their Holders to the Depositary for cancellation under the terms of the Deposit Agreement (except as specifically provided in the Deposit Agreement).

Notwithstanding anything contained in the Deposit Agreement or this ADR, in connection with the termination of the Deposit Agreement, the Depositary may, independently and without the need for any action by the Company, make available to Holders of ADSs a means to withdraw the Deposited Securities represented by their ADSs and to direct the deposit of such Deposited Securities into an unsponsored American depositary shares program established by the Depositary, upon such terms and conditions as the Depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored American depositary shares program under the Securities Act, and to receipt by the Depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the Depositary.

(25) **Compliance with and No Disclaimer under, U.S. Securities Laws.**

(a) Notwithstanding any provisions in this ADR or the Deposit Agreement to the contrary, the withdrawal or delivery of Deposited Securities will not be suspended by the Company or the Depositary except as would be permitted by Instruction I.A. (1) of the General Instructions to the Form F-6 Registration Statement, as amended from time to time, under the Securities Act.

(b) Each of the parties to the Deposit Agreement (including, without limitation, each Holder and Beneficial Owner) acknowledges and agrees that no provision of the Deposit Agreement or any ADR shall, or shall be deemed to, disclaim any liability under the Securities Act or the Exchange Act, in each case to the extent established under applicable U.S. laws.

(26) **No Third Party Beneficiaries/Acknowledgements**. The Deposit Agreement is for the exclusive benefit of the parties hereto (and their successors) and shall not be deemed to give any legal or equitable right, remedy or claim whatsoever to any other person, except to the extent specifically set forth in the Deposit Agreement. Nothing in the Deposit Agreement shall be deemed to give rise to a partnership or joint venture among the parties nor establish a fiduciary or similar relationship among the parties. The parties hereto acknowledge and agree that (i) Citibank and its Affiliates may at any time have multiple banking relationships with the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (ii) Citibank and its Affiliates may own and deal in any class of securities of the Company and its Affiliates and in ADSs, and may be engaged at any time in transactions in which parties adverse to the Company, the Holders, the Beneficial Owners or their respective Affiliates may have interests, (iii) the Depositary and its Affiliates may from time to time have in their possession non-public information about the Company, the Holders, the Beneficial Owners, and their respective Affiliates, (iv) nothing contained in the Deposit Agreement shall (a) preclude Citibank or any of its Affiliates from engaging in such transactions or establishing or maintaining such relationships, or (b) obligate Citibank or any of its Affiliates to disclose such information, transactions or relationships, or to account for any profit made or payment received in such transactions or relationships, (v) the Depositary shall not be deemed to have knowledge of any information any other division of Citibank or any of its Affiliates may have about the Company, the Holders, the Beneficial Owners, or any of their respective Affiliates, and (vi) the Company, the Depositary, the Custodian and their respective agents and controlling persons may be subject to the laws and regulations of jurisdictions other than the U.S. and England and Wales, and the authority of courts and regulatory authorities of such other jurisdictions, and, consequently, the requirements and the limitations of such other laws and regulations, and the decisions and orders of such other courts and regulatory authorities, may affect the rights and obligations of the parties to the Deposit Agreement.

(27) **Governing Law / Waiver of Jury Trial**. The Deposit Agreement and the ADRs shall be interpreted in accordance with, and all rights hereunder and thereunder and provisions hereof and thereof shall be governed by, the laws of the State of New York applicable to contracts made and to be wholly performed in that State. Notwithstanding anything contained in the Deposit Agreement, any ADR or any present or future provisions of the laws of the State of New York, the rights of holders of Shares and of any other Deposited Securities and the obligations and duties of the Company in respect of the holders of Shares and other Deposited Securities, as such, shall be governed by the laws of England and Wales (or, if applicable, such other laws as may govern the Deposited Securities).

EACH OF THE PARTIES TO THE DEPOSIT AGREEMENT (INCLUDING, WITHOUT LIMITATION, EACH HOLDER AND BENEFICIAL OWNER) IRREVOCABLY WAIVES, TO THE FULLEST EXTENT PERMITTED BY APPLICABLE LAW, ANY AND ALL RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING AGAINST THE COMPANY AND/OR THE DEPOSITARY ARISING OUT OF, OR RELATING TO, THE DEPOSIT AGREEMENT, ANY ADR AND ANY TRANSACTIONS CONTEMPLATED THEREIN (WHETHER BASED ON CONTRACT, TORT, COMMON LAW OR OTHERWISE).

(ASSIGNMENT AND TRANSFER SIGNATURE LINES)

FOR VALUE RECEIVED, the undersigned Holder hereby sell(s), assign(s) and transfer(s) unto _____ whose taxpayer identification number is _____ and whose address including postal zip code is _____, the within ADR and all rights thereunder, hereby irrevocably constituting and appointing _____ attorney-in-fact to transfer said ADR on the books of the Depositary with full power of substitution in the premises.

Dated:

Name: _____
By:
Title:

NOTICE: The signature of the Holder to this assignment must correspond with the name as written upon the face of the within instrument in every particular, without alteration or enlargement or any change whatsoever.

If the endorsement be executed by an attorney, executor, administrator, trustee or guardian, the person executing the endorsement must give his/her full title in such capacity and proper evidence of authority to act in such capacity, if not on file with the Depositary, must be forwarded with this ADR.

_____
SIGNATURE GUARANTEED

All endorsements or assignments of ADRs must be guaranteed by a member of a Medallion Signature Program approved by the Securities Transfer Association, Inc.

Legends

[The ADRs issued in respect of Partial Entitlement American Depositary Shares shall bear the following legend on the face of the ADR: "This ADR evidences ADSs representing 'partial entitlement' Shares of Orchard Therapeutics plc and as such do not entitle the holders thereof to the same per-share entitlement as other Shares (which are 'full entitlement' Shares) issued and outstanding at such time. The ADSs represented by this ADR shall entitle holders to distributions and entitlements identical to other ADSs when the Shares represented by such ADSs become 'full entitlement' Shares."]

EXHIBIT B

FEE SCHEDULE

ADS FEES AND RELATED CHARGES

All capitalized terms used but not otherwise defined herein shall have the meaning given to such terms in the Deposit Agreement.

I. ADS Fees

The following ADS fees are payable under the terms of the Deposit Agreement:

Service	Rate	By Whom Paid
(1)Issuance of ADSs (*e.g.*, an issuance upon a deposit of Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason), excluding issuances as a result of distributions described in paragraph (4) below.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) issued.	Person for whom ADSs are issued.
(2)Cancellation of ADSs (*e.g.*, a cancellation of ADSs for Delivery of deposited Shares, upon a change in the ADS(s)-to-Share(s) ratio, or for any other reason).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) cancelled.	Person for whom ADSs are being cancelled.
(3)Distribution of cash dividends or other cash distributions (*e.g.*, upon a sale of rights and other entitlements).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
(4)Distribution of ADSs pursuant to (i) stock dividends or other free stock distributions, or (ii) an exercise of rights to purchase additional ADSs.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
(5)Distribution of securities other than ADSs or rights to purchase additional ADSs (*e.g.*, spin-off shares).	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held.	Person to whom the distribution is made.
6)ADS Services.	Up to U.S. $5.00 per 100 ADSs (or fraction thereof) held on the applicable record date(s) established by the Depositary.	Person holding ADSs on the applicable record date(s) established by the Depositary.

II. Charges

The Company, Holders, Beneficial Owners, persons depositing Shares or withdrawing Deposited Securities in connection with ADS issuances and cancellations, and persons for whom ADSs are issued or cancelled shall be responsible for the following ADS charges under the terms of the Deposit Agreement:

(i) taxes (including applicable interest and penalties) and other governmental charges;

(ii) such registration fees as may from time to time be in effect for the registration of Shares or other Deposited Securities on the share register and applicable to transfers of Shares or other Deposited Securities to or from the name of the Custodian, the Depositary or any nominees upon the making of deposits and withdrawals, respectively;

(iii) such cable, telex and facsimile transmission and delivery expenses as are expressly provided in the Deposit Agreement to be at the expense of the person depositing Shares or withdrawing Deposited Property or of the Holders and Beneficial Owners of ADSs;

(iv) the expenses and charges incurred by the Depositary in the conversion of foreign currency (including transaction spreads);

(v) such fees and expenses as are incurred by the Depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to Deposited Property, ADSs and ADRs; and

(vi) the fees and expenses incurred by the Depositary, the Custodian, or any nominee in connection with the servicing or delivery of Deposited Property.

Exhibit 4.3

ORCHARD THERAPEUTICS PLC

2018 SHARE OPTION AND INCENTIVE PLAN

SECTION 1. GENERAL PURPOSE OF THE PLAN; DEFINITIONS

The name of the plan is the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "**Plan**"). The purpose of the Plan is to encourage and enable the officers, employees, Non-Employee Directors and Consultants of Orchard Therapeutics plc (the "**Company**") and its Affiliates upon whose judgment, initiative and efforts the Company largely depends for the successful conduct of its businesses to acquire a proprietary interest in the Company. It is anticipated that providing such persons with a direct stake in the Company's welfare will assure a closer identification of their interests with those of the Company and its shareholders, thereby stimulating their efforts on the Company's behalf and strengthening their desire to remain with the Company.

The following terms shall be defined as set forth below:

"Administrator" means either the Board or the remuneration committee of the Board or a similar committee performing the functions of the remuneration committee and which is comprised of not less than two Non-Employee Directors who are independent.

"*ADSs*" means American Depositary Shares, representing Ordinary Shares on deposit with a U.S. banking institution selected by the Company.

"*Affiliate*" means, at the time of determination, any "parent" or "subsidiary" of the Company as such terms are defined in Rule 405 of the U.S. Securities Act. The Board will have the authority to determine the time or times at which "parent" or "subsidiary" status is determined within the foregoing definition.

"Award" or *"Awards,"* except where referring to a particular category of grant under the Plan, shall include Incentive Share Options, Non-Qualified Share Options, Share Appreciation Rights, Restricted Share Units, Restricted Share Awards, Unrestricted Share Awards, Cash-Based Awards, and Dividend Equivalent Rights.

"Award Certificate" means a written or electronic document setting forth the terms and provisions applicable to an Award granted under the Plan. Each Award Certificate is subject to the terms and conditions of the Plan.

"Board" means the Board of Directors of the Company.

"Cash-Based Award" means an Award entitling the recipient to receive a cash-denominated payment.

"*Consultant*" means a consultant or adviser who provides *bona fide* services to the Company or an Affiliate as an independent contractor and who qualifies as a consultant or advisor under Instruction A.1.(a)(1) of Form S-8 under the U.S. Securities Act.

"*Dividend Equivalent Right*" means an Award entitling the grantee to receive credits based on cash dividends that would have been paid on the Shares specified in the Dividend Equivalent Right (or other award to which it relates) if such shares had been issued to and held by the grantee.

"*Effective Date*" means the date on which the Plan becomes effective as set forth in Section 21.

"*Fair Market Value*" of the Shares on any given date means the fair market value of the Shares determined in good faith by the Administrator; provided, however, that if the ADSs are listed on the National Association of Securities Dealers Automated Quotation System ("**NASDAQ**"), NASDAQ Global Market, The New York Share Exchange or another national securities exchange or traded on any established market, the determination shall be made by reference to market quotations. If there are no market quotations for such date, the determination shall be made by reference to the last date preceding such date for which there are market quotations; provided further, however, that if the date for which Fair Market Value is determined is the Registration Date, the Fair Market Value shall be the "Price to the Public" (or equivalent) set forth on the cover page for the final prospectus relating to the Company's initial public offering.

"*Incentive Share Option*" means any Share Option designated and qualified as an "incentive stock option" as defined in Section 422 of the U.S. Code.

"*Non-Employee Director*" means a member of the Board who is not also an employee of the Company or any Subsidiary.

"*Non-Qualified Share Option*" means any Share Option that is not an Incentive Share Option.

"*Option*" or "*Share Option*" means any option to purchase Shares granted pursuant to Section 5.

"*Ordinary Shares*" mean ordinary shares in the Company, with a nominal value of £0.00001 per share, subject to adjustments pursuant to Section 3.

"*Registration Date*" means the date upon which the registration statement on Form S-1 that is filed by the Company with respect to its initial public offering is declared effective by the Securities and Exchange Commission.

"*Restricted Shares*" means the Shares underlying a Restricted Share Award that remain subject to a risk of forfeiture or the Company's right of repurchase.

"*Restricted Share Award*" means an Award of Restricted Shares subject to such restrictions and conditions as the Administrator may determine at the time of grant.

"*Restricted Share Units*" means an Award of Share units subject to such restrictions and conditions as the Administrator may determine at the time of grant.

"*Sale Event*" shall mean (i) the sale of all or substantially all of the assets of the Company on a consolidated basis to an unrelated person or entity, (ii) a merger, reorganization or consolidation pursuant to which the holders of the Company's outstanding voting power and outstanding Share immediately prior to such transaction do not own a majority of the outstanding voting power and outstanding Share or other equity interests of the resulting or successor entity (or its ultimate parent, if applicable) immediately upon completion of such transaction, (iii) the sale of all of the Share of the Company to an unrelated person, entity or group thereof acting in concert, or (iv) any other transaction in which the owners of the Company's outstanding voting power immediately prior to such transaction do not own at least a majority of the outstanding voting power of the Company or any successor entity immediately upon completion of the transaction other than as a result of the acquisition of securities directly from the Company.

"*Sale Price*" means the value as determined by the Administrator of the consideration payable, or otherwise to be received by shareholders, per Share pursuant to a Sale Event.

"*Section 409A*" means Section 409A of the U.S. Code and the regulations and other guidance promulgated thereunder.

"*Share*" means an Ordinary Share and/or the number of ADSs equal to an Ordinary Share, as the context may require.

"*Share Appreciation Right*" means an Award entitling the recipient to receive Shares (or cash, to the extent explicitly provided for in the applicable Award Certificate) having a value equal to the excess of the Fair Market Value of the Share on the date of exercise over the exercise price of the Share Appreciation Right multiplied by the number of Shares with respect to which the Share Appreciation Right shall have been exercised.

"*Subsidiary*" means any corporation or other entity (other than the Company) in which the Company has at least a 50 percent interest, either directly or indirectly.

"*Ten Percent Owner*" means an employee who owns or is deemed to own (by reason of the attribution rules of Section 424(d) of the U.S. Code) more than 10 percent of the combined voting power of all classes of Share of the Company or any parent or subsidiary corporation.

"*Unrestricted Share Award*" means an Award of Shares free of any restrictions.

"*U.S. Code*" means the Internal Revenue Code of 1986, as amended, and any successor Code, and related rules, regulations and interpretations.

"*U.S. Exchange Act*" means the Securities Exchange Act of 1934, as amended, and the rules and regulations thereunder.

"*U.S. Securities Act*" means the U.S. Securities Act of 1933, as amended, and the rules and regulations thereunder.

SECTION 2. ADMINISTRATION OF PLAN; ADMINISTRATOR AUTHORITY TO SELECT GRANTEES AND DETERMINE AWARDS

(a) Administration of Plan. The Plan shall be administered by the Administrator.

(b) Powers of Administrator. The Administrator shall have the power and authority to grant Awards consistent with the terms of the Plan, including the power and authority:

(i) to select the individuals to whom Awards may from time to time be granted;

(ii) to determine the time or times of grant, and the extent, if any, of Incentive Share Options, Non-Qualified Share Options, Share Appreciation Rights, Restricted Share Awards, Restricted Share Units, Unrestricted Share Awards, Cash-Based Awards, and Dividend Equivalent Rights, or any combination of the foregoing, granted to any one or more grantees;

(iii) to determine the number of Shares to be covered by any Award;

(iv) to determine and modify from time to time the terms and conditions, including restrictions, not inconsistent with the terms of the Plan, of any Award, which terms and conditions may differ among individual Awards and grantees, and to approve the forms of Award Certificates;

(v) to accelerate at any time the exercisability or vesting of all or any portion of any Award;

(vi) subject to the provisions of Section 5(c), to extend at any time the period in which Share Options may be exercised; and

(vii) at any time to adopt, alter and repeal such rules, guidelines and practices for administration of the Plan and for its own acts and proceedings as it shall deem advisable; to interpret the terms and provisions of the Plan and any Award (including related written instruments); to make all determinations it deems advisable for the administration of the Plan; to decide all disputes arising in connection with the Plan; and to otherwise supervise the administration of the Plan.

All decisions and interpretations of the Administrator shall be binding on all persons, including the Company and Plan grantees.

(c) Delegation of Authority to Grant Awards. Subject to applicable law, the Administrator, in its discretion, may delegate to a committee consisting of one or more officers of the Company all or part of the Administrator's authority and duties with respect to the granting of Awards to individuals who are (i) not subject to the reporting and other provisions of Section 16 of the U.S. Exchange Act, as applicable, and (ii) not members of the delegated committee. Any such delegation by the Administrator shall include a limitation as to the amount of Share underlying Awards that may be granted during the period of the delegation and shall contain guidelines as to the determination of the exercise price and the vesting criteria. The Administrator may revoke or amend the terms of a delegation at any time but such action shall not invalidate any prior actions of the Administrator's delegate or delegates that were consistent with the terms of the Plan.

(d) Award Certificate. Awards under the Plan shall be evidenced by Award Certificates that set forth the terms, conditions and limitations for each Award which may include, without limitation, the term of an Award and the provisions applicable in the event employment or service terminates.

(e) Indemnification. Neither the Board nor the Administrator, nor any member of either or any delegate thereof, shall be liable for any act, omission, interpretation, construction or determination made in good faith in connection with the Plan, and the members of the Board and the Administrator (and any delegate thereof) shall be entitled in all cases to indemnification and reimbursement by the Company in respect of any claim, loss, damage or expense (including, without limitation, reasonable attorneys' fees) arising or resulting therefrom to the fullest extent permitted by law and/or under the Company's articles or bylaws or any directors' and officers' liability insurance coverage which may be in effect from time to time and/or any indemnification agreement between such individual and the Company.

(f) Foreign Award Recipients. Notwithstanding any provision of the Plan to the contrary, in order to comply with the laws in other countries in which the Company and its Subsidiaries operate or have employees or other individuals eligible for Awards, the Administrator, in its sole discretion, shall have the power and authority to: (i) determine which Subsidiaries shall be covered by the Plan; (ii) determine which individuals outside the United States are eligible to participate in the Plan; (iii) modify the terms and conditions of any Award granted to individuals outside the United States to comply with applicable foreign laws; (iv) establish subplans and modify exercise procedures and other terms and procedures, to the extent the Administrator determines such actions to be necessary or advisable (and such subplans and/or modifications shall be attached to this Plan as appendices); provided, however, that no such subplans and/or modifications shall increase the share limitations contained in Section 3(a) hereof; and (v) take any action, before or after an Award is made, that the Administrator determines to be necessary or advisable to obtain approval or comply with any local governmental regulatory exemptions or approvals. Notwithstanding the foregoing, the Administrator may not take any actions hereunder, and no Awards shall be granted, that would violate the U.S. Exchange Act or any other applicable United States securities law, the U.S. Code, or any other applicable United States governing statute or law.

SECTION 3. SHARES ISSUABLE UNDER THE PLAN; MERGERS; SUBSTITUTION

(a) Shares Issuable. The maximum number of Shares reserved and available for issuance under the Plan shall be 4,254,741 Shares (the "**Initial Limit**"), subject to adjustment as provided in Section 3(b), plus on January 1, 2019 and each January 1 thereafter, the number of Shares reserved and available for issuance under the Plan shall be cumulatively increased by five percent (5%) of the number of Shares issued and outstanding on the immediately preceding December 31, or such lesser number as the Administrator may determine (the "**Annual Increase**"). Subject to such overall limitation, the maximum aggregate number of Shares that may be issued in the form of Incentive Share Options shall not exceed the Initial Limit cumulatively increased on January 1, 2019 and on each January 1 thereafter by the lesser of the Annual Increase for such year or 4,254,741 Shares, subject in all cases to adjustment as provided in Section 3(b).For purposes of this limitation, the Shares underlying any awards under Plan or the Orchard Therapeutics plc 2016 Employee Share Option Plan that are forfeited, canceled, held

back upon exercise of an Option or settlement of an Award to cover the exercise price or tax withholding, reacquired by the Company prior to vesting, satisfied without the issuance of Shares or otherwise terminated (other than by exercise) shall be added back to the Shares available for issuance under the Plan and, to the extent permitted under Section 422 of the U.S. Code and the regulations promulgated thereunder, the Shares that may be issued as Incentive Share Options. In the event the Company repurchases Shares on the open market, such Shares shall not be added to the Shares available for issuance under the Plan. Subject to such overall limitations, Shares may be issued up to such maximum number pursuant to any type or types of Award. The shares available for issuance under the Plan may be authorized but unissued Shares or Shares reacquired by the Company.

(b) Changes in Shares. Subject to Section 3(c) hereof, if, as a result of any reorganization, recapitalization, reclassification, share dividend, share split, reverse share split or other similar change in the Company's capital shares, the outstanding Shares are increased or decreased or are exchanged for a different number or kind of shares or other securities of the Company, or additional shares or new or different shares or other securities of the Company or other non-cash assets are distributed with respect to such Shares or other securities, or, if, as a result of any merger or consolidation, sale of all or substantially all of the assets of the Company, the outstanding Shares are converted into or exchanged for securities of the Company or any successor entity (or a parent or subsidiary thereof), the Administrator shall make an appropriate or proportionate adjustment in (i) the maximum number of shares reserved for issuance under the Plan, including the maximum number of shares that may be issued in the form of Incentive Share Options, (ii) the number and kind of shares or other securities subject to any then outstanding Awards under the Plan, (iii) the repurchase price, if any, per share subject to each outstanding Restricted Share Award, and (iv) the exercise price for each share subject to any then outstanding Share Options and Share Appreciation Rights under the Plan, without changing the aggregate exercise price (i.e., the exercise price multiplied by the number of Share Options and Share Appreciation Rights) as to which such Share Options and Share Appreciation Rights remain exercisable. The Administrator shall also make equitable or proportionate adjustments in the number of shares subject to outstanding Awards and the exercise price and the terms of outstanding Awards to take into consideration cash dividends paid other than in the ordinary course or any other extraordinary corporate event. The adjustment by the Administrator shall be final, binding and conclusive. No fractional Shares shall be issued under the Plan resulting from any such adjustment, but the Administrator in its discretion may make a cash payment in lieu of fractional shares.

(c) Mergers and Other Transactions. In the case of and subject to the consummation of a Sale Event, the parties thereto may cause the assumption or continuation of Awards theretofore granted by the successor entity, or the substitution of such Awards with new Awards of the successor entity or parent thereof, with appropriate adjustment as to the number and kind of shares and, if appropriate, the per share exercise prices, as such parties shall agree. To the extent the parties to such Sale Event do not provide for the assumption, continuation or substitution of Awards, upon the effective time of the Sale Event, the Plan and all outstanding Awards granted hereunder shall terminate. In such case, except as may be otherwise provided in the relevant Award Certificate, all Options and Share Appreciation Rights that are not exercisable immediately prior to the effective time of the Sale Event shall become fully exercisable as of the effective time of the Sale Event, all other Awards with time-based vesting,

conditions or restrictions shall become fully vested and nonforfeitable as of the effective time of the Sale Event, and all Awards with conditions and restrictions relating to the attainment of performance goals may become vested and nonforfeitable in connection with a Sale Event in the Administrator's discretion or to the extent specified in the relevant Award Certificate. In the event of such termination, (i) the Company shall have the option (in its sole discretion) to make or provide for a payment, in cash or in kind, to the grantees holding Options and Share Appreciation Rights, in exchange for the cancellation thereof, in an amount equal to the difference between (A) the Sale Price multiplied by the number of Shares subject to outstanding Options and Share Appreciation Rights (to the extent then exercisable at prices not in excess of the Sale Price) and (B) the aggregate exercise price of all such outstanding Options and Share Appreciation Rights (provided that, in the case of an Option or Share Appreciation Right with an exercise price equal to or less than the Sale Price, such Option or Share Appreciation Right shall be cancelled for no consideration); or (ii) each grantee shall be permitted, within a specified period of time prior to the consummation of the Sale Event as determined by the Administrator, to exercise all outstanding Options and Share Appreciation Rights (to the extent then exercisable) held by such grantee. The Company shall also have the option (in its sole discretion) to make or provide for a payment, in cash or in kind, to the grantees holding other Awards in an amount equal to the Sale Price multiplied by the number of vested Shares under such Awards.

SECTION 4. ELIGIBILITY

Grantees under the Plan will be such employees, Non-Employee Directors and Consultants of the Company and its Affiliates as are selected from time to time by the Administrator in its sole discretion; provided that Awards may not be granted to employees, Directors and Consultants who are providing services only to any "parent" of the Company, as such term is defined in Rule 405 of the U.S. Securities Act, unless (i) the Shares underlying the Awards is treated as "service recipient stock" under Section 409A or (ii) the Company, in consultation with its legal counsel, has determined that such Awards are exempt from or otherwise comply with Section 409A.

SECTION 5. SHARE OPTIONS

(a) Award of Share Options. The Administrator may grant Share Options under the Plan. Any Share Option granted under the Plan shall be in such form as the Administrator may from time to time approve.

Share Options granted under the Plan may be either Incentive Share Options or Non-Qualified Share Options. Incentive Share Options may be granted only to employees of the Company or any Subsidiary that is a "subsidiary corporation" within the meaning of Section 424(f) of the U.S. Code. To the extent that any Option does not qualify as an Incentive Share Option, it shall be deemed a Non-Qualified Share Option.

Share Options granted pursuant to this Section 5 shall be subject to the following terms and conditions and shall contain such additional terms and conditions, not inconsistent with the terms of the Plan, as the Administrator shall deem desirable. If the Administrator so determines, Share Options may be granted in lieu of cash compensation at the optionee's election, subject to such terms and conditions as the Administrator may establish.

(b) Exercise Price. The exercise price per Share covered by a Share Option granted pursuant to this Section 5 shall be determined by the Administrator at the time of grant but shall not be less than 100 percent of the Fair Market Value on the date of grant. In the case of an Incentive Share Option that is granted to a Ten Percent Owner, the option price of such Incentive Share Option shall be not less than 110 percent of the Fair Market Value on the grant date. Notwithstanding the foregoing, Share Options may be granted with an exercise price per share that is less than 100 percent of the Fair Market Value on the date of grant (i) pursuant to a transaction described in, and in a manner consistent with, Section 424(a) of the U.S. Code or (ii) to individuals who are not subject to U.S. income tax.

(c) Option Term. The term of each Share Option shall be fixed by the Administrator, but no Share Option shall be exercisable more than ten years after the date the Share Option is granted. In the case of an Incentive Share Option that is granted to a Ten Percent Owner, the term of such Share Option shall be no more than five years from the date of grant.

(d) Exercisability; Rights of a Shareholder. Share Options shall become exercisable at such time or times, whether or not in installments, as shall be determined by the Administrator at or after the grant date. The Administrator may at any time accelerate the exercisability of all or any portion of any Share Option. An optionee shall have the rights of a shareholder only as to shares acquired upon the exercise of a Share Option and not as to unexercised Share Options.

(e) Method of Exercise. Share Options may be exercised in whole or in part, by giving written or electronic notice of exercise to the Company, specifying the number of shares to be purchased. Payment of the purchase price may be made by one or more of the following methods except to the extent otherwise provided in the Option Award Certificate:

(i) In cash, by certified or bank check or other instrument acceptable to the Administrator;

(ii) Through the delivery (or attestation to the ownership following such procedures as the Company may prescribe) of Shares that are not then subject to restrictions under any Company plan. Such surrendered shares shall be valued at Fair Market Value on the exercise date;

(iii) By the optionee delivering to the Company a properly executed exercise notice together with irrevocable instructions to a broker to promptly deliver to the Company cash or a check payable and acceptable to the Company for the purchase price; provided that in the event the optionee chooses to pay the purchase price as so provided, the optionee and the broker shall comply with such procedures and enter into such agreements of indemnity and other agreements as the Company shall prescribe as a condition of such payment procedure; or

(iv) With respect to Share Options that are not Incentive Share Options, by a "net exercise" arrangement pursuant to which the Company will reduce the number of Shares issuable upon exercise by the largest whole number of shares with a Fair Market Value that does not exceed the aggregate exercise price.

Payment instruments will be received subject to collection. The transfer to the optionee on the records of the Company or of the transfer agent of the Shares to be purchased pursuant to the exercise of a Share Option will be contingent upon receipt from the optionee (or a purchaser acting in his stead in accordance with the provisions of the Share Option) by the Company of the full purchase price for such shares and the fulfillment of any other requirements contained in the Option Award Certificate or applicable provisions of laws (including the satisfaction of any withholding taxes that the Company is obligated to withhold with respect to the optionee). In the event an optionee chooses to pay the purchase price by previously-owned Shares through the attestation method, the number of Shares transferred to the optionee upon the exercise of the Share Option shall be net of the number of attested shares. In the event that the Company establishes, for itself or using the services of a third party, an automated system for the exercise of Share Options, such as a system using an internet website or interactive voice response, then the paperless exercise of Share Options may be permitted through the use of such an automated system.

(f) Annual Limit on Incentive Share Options. To the extent required for "incentive stock option" treatment under Section 422 of the U.S. Code, the aggregate Fair Market Value (determined as of the time of grant) of the Shares with respect to which Incentive Share Options granted under this Plan and any other plan of the Company or its parent and subsidiary corporations become exercisable for the first time by an optionee during any calendar year shall not exceed $100,000. To the extent that any Share Option exceeds this limit, it shall constitute a Non-Qualified Share Option.

SECTION 6. SHARE APPRECIATION RIGHTS

(a) Award of Share Appreciation Rights. The Administrator may grant Share Appreciation Rights under the Plan. A Share Appreciation Right is an Award entitling the recipient to receive Shares (or cash, to the extent explicitly provided for in the applicable Award Certificate) having a value equal to the excess of the Fair Market Value of a Share on the date of exercise over the exercise price of the Share Appreciation Right multiplied by the number of Shares with respect to which the Share Appreciation Right shall have been exercised.

(b) Exercise Price of Share Appreciation Rights. The exercise price of a Share Appreciation Right shall not be less than 100 percent of the Fair Market Value of the Share on the date of grant.

(c) Grant and Exercise of Share Appreciation Rights. Share Appreciation Rights may be granted by the Administrator independently of any Share Option granted pursuant to Section 5 of the Plan.

(d) Terms and Conditions of Share Appreciation Rights. Share Appreciation Rights shall be subject to such terms and conditions as shall be determined on the date of grant by the Administrator. The term of a Share Appreciation Right may not exceed ten years. The terms and conditions of each such Award shall be determined by the Administrator, and such terms and conditions may differ among individual Awards and grantees.

SECTION 7. RESTRICTED SHARE AWARDS

(a) Nature of Restricted Share Awards. The Administrator may grant Restricted Share Awards under the Plan. A Restricted Share Award is any Award of Restricted Shares subject to such restrictions and conditions as the Administrator may determine at the time of grant. Conditions may be based on continuing employment (or other service relationship) and/or achievement of pre-established performance goals and objectives.

(b) Rights as a Shareholder. Upon the grant of the Restricted Share Award and payment of any applicable purchase price, a grantee shall have the rights of a shareholder with respect to the voting of the Restricted Shares and receipt of dividends; provided that if the lapse of restrictions with respect to the Restricted Share Award is tied to the attainment of performance goals, any dividends paid by the Company during the performance period shall accrue and shall not be paid to the grantee until and to the extent the performance goals are met with respect to the Restricted Share Award. Unless the Administrator shall otherwise determine, (i) uncertificated Restricted Shares shall be accompanied by a notation on the records of the Company or the transfer agent to the effect that they are subject to forfeiture until such Restricted Shares are vested as provided in Section 7(d) below, and (ii) certificated Restricted Shares shall remain in the possession of the Company until such Restricted Shares are vested as provided in Section 7(d) below, and the grantee shall be required, as a condition of the grant, to deliver to the Company such instruments of transfer as the Administrator may prescribe.

(c) Restrictions. Restricted Shares may not be sold, assigned, transferred, pledged or otherwise encumbered or disposed of except as specifically provided herein or in the Restricted Share Award Certificate. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, if a grantee's employment (or other service relationship) with the Company and its Subsidiaries terminates for any reason, any Restricted Shares that have not vested at the time of termination shall automatically and without any requirement of notice to such grantee from or other action by or on behalf of, the Company be deemed to have been reacquired by the Company at its original purchase price (if any) from such grantee or such grantee's legal representative simultaneously with such termination of employment (or other service relationship), and thereafter shall cease to represent any ownership of the Company by the grantee or rights of the grantee as a shareholder. Following such deemed reacquisition of Restricted Shares that are represented by physical certificates, a grantee shall surrender such certificates to the Company upon request without consideration.

(d) Vesting of Restricted Shares. The Administrator at the time of grant shall specify the date or dates and/or the attainment of pre-established performance goals, objectives and other conditions on which the non-transferability of the Restricted Shares and the Company's right of repurchase or forfeiture shall lapse. Subsequent to such date or dates and/or the attainment of such pre-established performance goals, objectives and other conditions, the shares on which all restrictions have lapsed shall no longer be Restricted Shares and shall be deemed "vested."

SECTION 8. RESTRICTED SHARE UNITS

(a) Nature of Restricted Share Units. The Administrator may grant Restricted Share Units under the Plan. A Restricted Share Unit is an Award of share units that may be settled in Shares (or cash, to the extent explicitly provided for in the Award Certificate) upon the satisfaction of such restrictions and conditions at the time of grant. Conditions may be based on continuing employment (or other service relationship) and/or achievement of pre-established performance goals and objectives. The terms and conditions of each such Award shall be determined by the Administrator, and such terms and conditions may differ among individual Awards and grantees. Except in the case of Restricted Share Units with a deferred settlement date that complies with Section 409A, at the end of the vesting period, the Restricted Share Units, to the extent vested, shall be settled in the form of Shares. Restricted Share Units with deferred settlement dates are subject to Section 409A and shall contain such additional terms and conditions as the Administrator shall determine in its sole discretion in order to comply with the requirements of Section 409A.

(b) Election to Receive Restricted Share Units in Lieu of Compensation. The Administrator may, in its sole discretion, permit a grantee to elect to receive a portion of future cash compensation otherwise due to such grantee in the form of an award of Restricted Share Units. Any such election shall be made in writing and shall be delivered to the Company no later than the date specified by the Administrator and in accordance with Section 409A and such other rules and procedures established by the Administrator. Any such future cash compensation that the grantee elects to defer shall be converted to a fixed number of Restricted Share Units based on the Fair Market Value of a Share on the date the compensation would otherwise have been paid to the grantee if such payment had not been deferred as provided herein. The Administrator shall have the sole right to determine whether and under what circumstances to permit such elections and to impose such limitations and other terms and conditions thereon as the Administrator deems appropriate. Any Restricted Share Units that are elected to be received in lieu of cash compensation shall be fully vested, unless otherwise provided in the Award Certificate.

(c) Rights as a Shareholder. A grantee shall have the rights as a shareholder only as to Shares acquired by the grantee upon settlement of Restricted Share Units; provided, however, that the grantee may be credited with Dividend Equivalent Rights with respect to the share units underlying his Restricted Share Units, subject to the provisions of Section 11 and such terms and conditions as the Administrator may determine.

(d) Termination. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, a grantee's right in all Restricted Share Units that have not vested shall automatically terminate upon the grantee's termination of employment (or cessation of service relationship) with the Company and its Subsidiaries for any reason.

SECTION 9. UNRESTRICTED SHARE AWARDS

Grant or Sale of Unrestricted Share. The Administrator may grant (or sell at par value or such higher purchase price determined by the Administrator) an Unrestricted Share Award under the Plan. An Unrestricted Share Award is an Award pursuant to which the grantee may receive Shares of free of any restrictions under the Plan. Unrestricted Share Awards may be granted in respect of past services or other valid consideration, or in lieu of cash compensation due to such grantee.

SECTION 10. CASH-BASED AWARDS

Grant of Cash-Based Awards. The Administrator may grant Cash-Based Awards under the Plan. A Cash-Based Award is an Award that entitles the grantee to a payment in cash upon the attainment of specified performance goals. The Administrator shall determine the maximum duration of the Cash-Based Award, the amount of cash to which the Cash-Based Award pertains, the conditions upon which the Cash-Based Award shall become vested or payable, and such other provisions as the Administrator shall determine. Each Cash-Based Award shall specify a cash-denominated payment amount, formula or payment ranges as determined by the Administrator. Payment, if any, with respect to a Cash-Based Award shall be made in accordance with the terms of the Award and may be made in cash.

SECTION 11. DIVIDEND EQUIVALENT RIGHTS

(a) Dividend Equivalent Rights. The Administrator may grant Dividend Equivalent Rights under the Plan. A Dividend Equivalent Right is an Award entitling the grantee to receive credits based on cash dividends that would have been paid on the Shares specified in the Dividend Equivalent Right (or other Award to which it relates) if such shares had been issued to the grantee. A Dividend Equivalent Right may be granted hereunder to any grantee as a component of an award of Restricted Share Units or as a freestanding award. The terms and conditions of Dividend Equivalent Rights shall be specified in the Award Certificate. Dividend equivalents credited to the holder of a Dividend Equivalent Right may be paid currently or may be deemed to be reinvested in additional Shares, which may thereafter accrue additional equivalents. Any such reinvestment shall be at Fair Market Value on the date of reinvestment or such other price as may then apply under a dividend reinvestment plan sponsored by the Company, if any. Dividend Equivalent Rights may be settled in cash or Shares or a combination thereof, in a single installment or installments. A Dividend Equivalent Right granted as a component of an Award of Restricted Share Units shall provide that such Dividend Equivalent Right shall be settled only upon settlement or payment of, or lapse of restrictions on, such other Award, and that such Dividend Equivalent Right shall expire or be forfeited or annulled under the same conditions as such other Award.

(b) Termination. Except as may otherwise be provided by the Administrator either in the Award Certificate or, subject to Section 15 below, in writing after the Award is issued, a grantee's rights in all Dividend Equivalent Rights shall automatically terminate upon the grantee's termination of employment (or cessation of service relationship) with the Company and its Subsidiaries for any reason.

SECTION 12. TRANSFERABILITY OF AWARDS

(a) Transferability. Except as provided in Section 12 (b) below, during a grantee's lifetime, his or her Awards shall be exercisable only by the grantee, by the grantee's legal representative or guardian in the event of the grantee's incapacity (evidenced to the satisfaction of the Administrator) or the grantee's personal representatives in the case of his death. No Awards shall be sold, assigned, transferred or otherwise encumbered or disposed of by a grantee other than by will or by the laws of descent and distribution or pursuant to a domestic relations order. No Awards shall be subject, in whole or in part, to attachment, execution, or levy of any kind, and any purported transfer in violation hereof shall be null and void.

(b) Administrator Action. Notwithstanding Section 12(a), the Administrator, in its discretion, may provide either in the Award Certificate regarding a given Award or by subsequent written approval that the grantee (who is an employee or director) may transfer his or her Non-Qualified Share Options to his or her immediate family members, to trusts for the benefit of such family members, or to partnerships in which such family members are the only partners, provided that the transferee agrees in writing with the Company to be bound by all of the terms and conditions of this Plan and the applicable Award. In no event may an Award be transferred by a grantee for value.

(c) Family Member. For purposes of Section 12(b), "family member" shall mean a grantee's child, stepchild, grandchild, parent, stepparent, grandparent, spouse, former spouse, sibling, niece, nephew, mother-in-law, father-in-law, son-in-law, daughter-in-law, brother-in-law, or sister-in-law, including adoptive relationships, any person sharing the grantee's household (other than a tenant of the grantee), a trust in which these persons (or the grantee) have more than 50 percent of the beneficial interest, a foundation in which these persons (or the grantee) control the management of assets, and any other entity in which these persons (or the grantee) own more than 50 percent of the voting interests.

(d) Designation of Beneficiary. To the extent permitted by the Company, each grantee to whom an Award has been made under the Plan may designate a beneficiary or beneficiaries to exercise any Award or receive any payment under any Award payable on or after the grantee's death. Any such designation shall be on a form provided for that purpose by the Administrator and shall not be effective until received by the Administrator. If no beneficiary has been designated by a deceased grantee, or if the designated beneficiaries have predeceased the grantee, the beneficiary shall be the grantee's estate.

SECTION 13. TAX WITHHOLDING

(a) Payment by Grantee. If the Company or any Subsidiary is liable to account for tax (including Federal, state and local taxes and social security taxes in the US and their equivalent in any other jurisdiction) for which a grantee is liable by reason of the grant, release, exercise, assignment or surrender for consideration of an Award or the receipt of any benefit in connection with it, the Company and its Subsidiaries shall, to the extent permitted by the applicable law in the relevant jurisdiction, have the right to deduct any such taxes from any payment of any kind otherwise due to the grantee. The Company's obligation to deliver evidence of book entry (or share certificates) to any grantee is subject to and conditioned on tax withholding obligations being satisfied by the grantee.

(b) Payment in Shares. The Company's required tax withholding obligation may be satisfied, in whole or in part, by the Company withholding from Shares to be issued pursuant to any Award a number of shares with an aggregate Fair Market Value (as of the date the withholding is effected) that would satisfy the withholding amount due; provided, however, that the amount withheld does not exceed the maximum statutory tax rate or such lesser amount as is necessary to avoid liability accounting treatment. The Administrator may also require Awards to be subject to mandatory share withholding up to the required withholding amount. For purposes of share withholding, the Fair Market Value of withheld shares shall be determined in the same manner as the value of Shares includible in income of the Participants. The required tax withholding obligation may also be satisfied, in whole or in part, by an arrangement whereby a certain number of Shares issued pursuant to any Award are immediately sold and proceeds from such sale are remitted to the Company in an amount that would satisfy the withholding amount due.

(c) UK national insurance contributions. At the request of the Company or Subsidiary by which the relevant grantee is employed at any time before the vesting or exercise of an Award which is a Share Option, the grantee must either agree to meet or elect, to the extent lawfully permitted (and in the case of an election, using a form approved by HM Revenue & Customs) that the whole of the liability for any secondary class 1 (employers') national insurance contributions arising as a result of the grant, release, exercise, assignment or surrender for consideration of the Share Option, shall be borne by or transferred to the grantee.

SECTION 14. SECTION 409A AWARDS

To the extent that any Award is determined to constitute "nonqualified deferred compensation" within the meaning of Section 409A (a "**409A Award**"), the Award shall be subject to such additional rules and requirements as specified by the Administrator from time to time in order to comply with Section 409A. In this regard, if any amount under a 409A Award is payable upon a "separation from service" (within the meaning of Section 409A) to a grantee who is then considered a "specified employee" (within the meaning of Section 409A), then no such payment shall be made prior to the date that is the earlier of (i) six months and one day after the grantee's separation from service, or (ii) the grantee's death, but only to the extent such delay is necessary to prevent such payment from being subject to interest, penalties and/or additional tax imposed pursuant to Section 409A. Further, the settlement of any 409A Award may not be accelerated except to the extent permitted by Section 409A.

SECTION 15. TERMINATION OF EMPLOYMENT, TRANSFER, LEAVE OF ABSENCE, ETC.

(a) Termination of Employment. If the grantee's employer ceases to be a Subsidiary, the grantee shall be deemed to have terminated employment for purposes of the Plan.

(b) For purposes of the Plan, the following events shall not be deemed a termination of employment:

(i) a transfer to the employment of the Company from a Subsidiary or from the Company to a Subsidiary, or from one Subsidiary to another; or

(ii) an approved leave of absence for military service or sickness, or for any other purpose approved by the Company, if the employee's right to re-employment is guaranteed either by a statute or by contract or under the policy pursuant to which the leave of absence was granted or if the Administrator otherwise so provides in writing.

(c) In the case of grantees who are employed in the UK, the termination date of their employment shall be the date notice is given by or to them unless the Administrator decides that it can be a later date before the statutory or contractual expiry date of their notice period.

SECTION 16. AMENDMENTS AND TERMINATION

The Board may, at any time, amend or discontinue the Plan and the Administrator may, at any time, amend or cancel any outstanding Award for the purpose of satisfying changes in law or for any other lawful purpose, but no such action shall adversely affect rights under any outstanding Award without the holder's consent. The Administrator is specifically authorized to exercise its discretion to reduce the exercise price of outstanding Share Options or Share Appreciation Rights or effect the repricing of such Awards through cancellation and re-grants. To the extent required under the rules of any securities exchange or market system on which the Shares are listed, to the extent determined by the Administrator to be required by the U.S. Code to ensure that Incentive Share Options granted under the Plan are qualified under Section 422 of the U.S. Code, Plan amendments shall be subject to approval by the Company shareholders entitled to vote at a meeting of shareholders. Nothing in this Section 18 shall limit the Administrator's authority to take any action permitted pursuant to Section 3(b) or 3(c).

SECTION 17. STATUS OF PLAN

With respect to the portion of any Award that has not been exercised and any payments in cash, Shares or other consideration not received by a grantee, a grantee shall have no rights greater than those of a general creditor of the Company unless the Administrator shall otherwise expressly determine in connection with any Award or Awards. In its sole discretion, the Administrator may authorize the creation of trusts or other arrangements to meet the Company's obligations to deliver Shares or make payments with respect to Awards hereunder, provided that the existence of such trusts or other arrangements is consistent with the foregoing sentence.

SECTION 18. GENERAL PROVISIONS

(a) No Distribution. The Administrator may require each person acquiring Shares pursuant to an Award to represent to and agree with the Company in writing that such person is acquiring the shares without a view to distribution thereof.

(b) Issuance of Shares. To the extent certificated, Share certificates to grantees under this Plan shall be deemed delivered for all purposes when the Company or a transfer agent of the Company shall have mailed such certificates in the United States mail, addressed to the grantee, at the grantee's last known address on file with the Company. Uncertificated Shares shall be deemed delivered for all purposes when the Company or a transfer agent of the Company shall have given to the grantee by electronic mail (with proof of receipt) or by United States mail, addressed to the grantee, at the grantee's last known address on file with the Company, notice of issuance and recorded the issuance in its records (which may include electronic "book entry" records). Notwithstanding anything herein to the contrary, the Company shall not be required to issue or deliver any evidence of book entry or certificates evidencing Shares pursuant to the exercise or settlement of any Award, unless and until the Administrator has determined, with advice of counsel (to the extent the Administrator deems such advice necessary or advisable), that the issuance and delivery is in compliance with all applicable laws, regulations of governmental authorities and, if applicable, the requirements of any exchange on which the Shares are listed, quoted or traded. Any Shares issued pursuant to the Plan shall be subject to any stop-transfer orders and other restrictions as the Administrator deems necessary or advisable to comply with federal, state or foreign jurisdiction, securities or other laws, rules and quotation system on which the Shares are listed, quoted or traded. The Administrator may place legends on any Share certificate or notations on any book entry to reference restrictions applicable to the Shares. In addition to the terms and conditions provided herein, the Administrator may require that an individual make such reasonable covenants, agreements, and representations as the Administrator, in its discretion, deems necessary or advisable in order to comply with any such laws, regulations, or requirements. The Administrator shall have the right to require any individual to comply with any timing or other restrictions with respect to the settlement or exercise of any Award, including a window-period limitation, as may be imposed in the discretion of the Administrator.

(c) Shareholder Rights. Until Shares are deemed delivered in accordance with Section 20(b), no right to vote or receive dividends or any other rights of a shareholder will exist with respect to Shares to be issued in connection with an Award, notwithstanding the exercise of a Share Option or any other action by the grantee with respect to an Award.

(d) Other Compensation Arrangements; No Employment Rights. Nothing contained in this Plan shall prevent the Board from adopting other or additional compensation arrangements, including trusts, and such arrangements may be either generally applicable or applicable only in specific cases. The adoption of this Plan and the grant of Awards do not confer upon any employee any right to continued employment with the Company or any Subsidiary. If a grantee ceases to be employed by the Company or any Subsidiary for any reason whatsoever (including as a result of being wrongfully or unfairly dismissed) they shall not be entitled, and by accepting an Award they shall be deemed to have waived any possible entitlement, to any sum or other benefit accrued or in prospect in connection with that Award, and no such loss or curtailment shall form part of any claim for damages for breach of the grantee's contract of employment or compensation for dismissal or any other claim whatsoever.

(e) Trading Policy Restrictions. Option exercises and other Awards under the Plan shall be subject to the Company's insider trading policies and procedures, as in effect from time to time.

(f) Clawback Policy. Awards under the Plan shall be subject to the Company's clawback policy, as in effect from time to time.

SECTION 19. EFFECTIVE DATE OF PLAN

This Plan shall become effective upon the date immediately preceding the Registration Date following shareholder approval in accordance with applicable law, the Company's bylaws and articles of incorporation, and applicable stock exchange rules. No grants of Share Options and other Awards may be made hereunder after the tenth anniversary of the Effective Date and no grants of Incentive Share Options may be made hereunder after the tenth anniversary of the date the Plan is approved by the Board.

SECTION 20. GOVERNING LAW

This Plan and all Awards and actions taken thereunder shall be governed by, and construed in accordance with the law of England and Wales, applied without regard to conflict of law principles.

CERTAIN CONFIDENTIAL PORTIONS OF THIS EXHIBIT WERE OMITTED AND REPLACED WITH "[***]". A COMPLETE VERSION OF THIS EXHIBIT HAS BEEN FILED SEPARATELY WITH THE SECRETARY OF THE SECURITIES AND EXCHANGE COMMISSION PURSUANT TO AN APPLICATION REQUESTING CONFIDENTIAL TREATMENT PURSUANT TO RULE 24b-2PROMULGATED UNDER THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED.

S I N G L E – T E N A N T
C O M M E R C I A L / I N D U S T R I A L L E A S E (N N N)

800 Corporate Way
Fremont, CA

LANDLORD:

BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC,
a Delaware limited liability company

TENANT:

ORCHARD THERAPEUTICS NORTH AMERICA,
a California corporation

TABLE OF CONTENTS

EXHIBITS:

RIDERS:

THIS LEASE, entered into as of the 11th day of December, 2018 (the "**Effective Date**") for reference purposes, is by and between BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC, a Delaware limited liability company, hereinafter referred to as "**Landlord**", and ORCHARD THERAPEUTICS NORTH AMERICA, a California corporation, hereinafter referred to as "**Tenant**".

ARTICLE 1 - LEASE SUMMARY AND PROPERTY SPECIFIC PROVISIONS

1.1 **Landlord's Address**:c/o LBA Realty LLC
3347 Michelson Drive, Suite 200
Irvine, California 92612
Attn: Alison Vukovich
Telephone: (949) 955-9312
E-mail: leasingnotices@lbarealty.com

With copies to: LBA Realty LLC
3347 Michelson Drive, Suite 200
Irvine, California 92612
Attn: SVP - Operations
Telephone: (949) 833-0400
E-mail: leasingnotices@lbarealty.com

For payment of Rent: BPP Pac Ind CA NonREIT Owner 2 LLC
PO Box 741170
Los Angeles, CA 90074-1170

1.2 **Tenant's Address**: Orchard Therapeutics
2 Seaport Lane, Floor 8
Boston, Massachusetts 02210-2001
Attention: Chief Financial Officer

With copies to: Orchard Therapeutics Limited
108 Cannon Street
London EC4N 6EU
Attention: General Counsel

and

Orchard Therapeutics North America
To the Premises
Attn: Stewart Craig
Telephone: (831) 383-9736
E-mail: stewart.craig@orchard-tx.com

and
Dain Torpy
745 Atlantic Avenue
Boston, Massachusetts 02111
Attention: Orchard Therapeutics

Tenant Billing Address: Orchard Therapeutics
2 Seaport Lane, Floor 8
Boston, Massachusetts 02210-2001

1.3 **Building**: The Building commonly known as 800 Corporate Way containing approximately 152,995 rentable square feet, as depicted on Exhibit A attached hereto. Landlord and Tenant stipulate and agree that the aggregate rentable area of the Building is 152,995 rentable square feet, for all purposes of this Lease.

1.4 **Premises**: The Building and all improvements and facilities situated upon the land as depicted on Exhibit B attached hereto (the "**Property**"), including all drive aisles, parking areas, sidewalks, walls, landscaping and exterior improvements located on the Property, together with any appurtenant easements and privileges benefitting the Property.

1.5 **City**: The City of Fremont, County of Alameda, State of California.

1.6 **Commencement Date**: The later of execution of this Lease and the date that Landlord, Tenant and Landlord's Mortgagee agree upon and execute an SNDA as described in Article 26. The Estimated Commencement Date is December 15, 2018. The parties shall confirm the actual Commencement by Notice of Lease Term Dates as described in Section 4.1.

1.7 **Term**: One Hundred Thirty-eight (138) months, commencing on the Commencement Date and ending on May 31, 2030 ("**Expiration Date**").

1.8 **Monthly Base Rent**:

Months or Period	**Monthly Base Rent**
*12/1/18 – 1/31/19	$0.00
**2/1/19 – 7/31/19	Operating Expenses Only
8/1/19 – 7/31/20	$214,193.00
8/1/20 – 7/31/21	$220,618.79
8/1/21 – 7/31/22	$227,237.35
8/1/22 – 7/31/23	$234,054.47
8/1/23 – 7/31/24	$241,076.11
8/1/24 – 7/31/25	$248,308.39
8/1/25 – 7/31/26	$255,757.64
8/1/26 – 7/31/27	$263,430.37
8/1/27 – 7/31/28	$271,333.28
8/1/28 – 7/31/29	$279,473.28
8/1/29 – 5/31/30	$287,857.48

*Monthly Base Rent and Operating Expenses abated from December 1, 2018 through January 31, 2019.

Monthly Base Rent abated and Tenant to pay Operating Expenses (currently estimated at $0.27 per rentable square foot per month) only from February 1, 2019 through the earlier of (i) July 31, 2019 or (ii) the date when Tenant obtains a certificate of occupancy or equivalent authorization to occupy the Premises (the "Rent Commencement Date**"). Tenant shall commence payment of Monthly Base Rent on the Rent Commencement Date at the monthly rate of $214,193.00 (pro-rated for any partial month); provided, however, that the first annual Monthly Base Rent adjustment (i.e., to $220,618.79) shall occur on August 1, 2020 even if the Rent Commencement Date occurs before August 1, 2019.

1.9 **Letter of Credit**: $[***], subject to the terms and conditions of Article 6 below.

1.10 **Permitted Use**: General office, research and development, lab, manufacturing, marketing and other related legal uses, including storage and distribution, subject to the provisions set forth in this Lease and as permitted by law.

1.11 **Parking**: Subject to Article 11 of this Lease, during the Term, Tenant shall be entitled to utilize all on-site parking spaces upon the Premises, for vehicle parking and storage in compliance with all applicable Laws and zoning regulations. All responsibility for damage to or loss of vehicles is assumed by the parker except to the extent such damage is caused by the gross negligence or willful misconduct of Landlord or the Landlord Parties, and Landlord shall not be responsible for any such damage or loss by water, fire, defective brakes, the act or omissions of others, theft, or for any other cause.

1.12 **Brokers**: JLL representing Landlord and Newmark Cornish and Carey representing Tenant.

1.13 **Interest Rate**: The lesser of: (a) Ten percent (10%) or (b) the maximum rate permitted by law in the State where the Property is located.

1.14 **Insurance Amounts**:

a. **Commercial General Liability Insurance**: General liability of not less than One Million Dollars ($1,000,000.00) per occurrence and Two Million Dollars ($2,000,000.00) in the aggregate.

b. **Commercial Automobile Liability Insurance**: Limit of liability of not less than One Million Dollars ($1,000,000.00) per accident.

c. **Worker's Compensation and Employers Liability Insurance**: With limits as mandated pursuant to the laws in the State in which the Property is located, or One Million Dollars ($1,000,000.00) per person, disease and accident, whichever is greater.

d. **Umbrella Liability Insurance**: Limits of not less than Five Million Dollars ($5,000,000.00) per occurrence.

e. **Loss of Income, Extra Expense and Business Interruption Insurance:** In such amounts as will reimburse Tenant for 12 months of direct or indirect loss of earnings attributable to all perils commonly insured against by prudent tenants or attributable to prevention of access to the Premises, Tenant's parking areas or to the Building as a result of such perils.

1.15 **Tenant Improvement Allowance**: $[***] to be applied and disbursed as provided in the Work Letter, with an additional Roof Allowance of $[***] and HVAC Allowance of [$[***]] to be applied and disbursed as provided in Section 4.4 below.

1.16 **Operating Expenses, Insurance Costs, Taxes and Management Fee; Triple Net Lease**. Except as otherwise provided herein, all Rent (as that term is defined under Section 5.2 of the Standard Lease Provisions) shall be absolutely net to Landlord so that this Lease shall yield net to Landlord the Rent to be paid each month during the Term of this Lease. Accordingly, and except as otherwise provided in this Lease, all costs, expenses and obligations of every kind or nature whatsoever relating to the Premises which may arise or become due during the Term of this Lease including, without limitation, all costs and expenses of operation, maintenance, repairs and replacements of the Premises, if any, to the extent not paid directly by Tenant pursuant to this Lease, Insurance Costs and Taxes relating to the Premises, together with a monthly management fee to Landlord equal to [***] (the "**Management Fee**") (collectively, "**Operating Expenses**") shall be paid by Tenant monthly as additional rent as provided below. Nothing herein contained shall be deemed to require Tenant to pay or discharge any liens or mortgages of any character whatsoever which may exist or hereafter be placed upon the Premises by an affirmative act or omission of (i) Landlord or its agents, employees, contractors or (ii) any prior tenants or occupants of the Building.

a. **Estimate Statement**. By the first day of each calendar year during the Term (or as soon as practicable thereafter), Landlord shall deliver to Tenant a statement ("**Estimate Statement**") estimating Insurance Costs, Taxes and the Management Fee for the current calendar year pro rated into monthly installments. If at any time during the Term, but not more often than once each calendar year, Landlord reasonably determines that the estimated amount of Insurance Costs, Management Fee and/or Taxes payable by Tenant for the current calendar year will be greater or less than the amount set forth in the then current Estimate Statement, Landlord may issue a revised Estimate Statement and Tenant agrees to pay Landlord, within thirty (30) days after receipt of the revised Estimate Statement, the difference between the amount owed by Tenant under such revised Estimate Statement and the amount owed by Tenant under the original Estimate Statement for the portion of the then current calendar year which has expired. Thereafter Tenant agrees to pay Insurance Costs, Management Fee and Taxes based on such revised Estimate Statement until Tenant receives the next calendar year's Estimate Statement or a new revised Estimate Statement for the current calendar year concurrently with the regular monthly Rent payments for the balance of the calendar year and shall continue until the next calendar year's Estimate Statement (or current calendar year's revised Estimate Statement) is received.

b. **Actual Statement**. By the first day of May (or as soon as practicable thereafter) of each subsequent calendar year during the Term, Landlord shall deliver to Tenant a statement ("**Actual Statement**") which states the actual Operating Expenses payable by Tenant for the immediately preceding calendar year. If the Actual Statement reveals that the actual Operating Expenses were more than the corresponding costs actually paid by Tenant with respect to the preceding calendar year, Tenant agrees to pay Landlord the difference in a lump sum within thirty (30) days after receipt of the Actual Statement. If the Actual Statement reveals that the actual Operating Expenses were less than the corresponding costs actually paid by Tenant with respect to the preceding calendar year, Landlord will, at Tenant's election, either credit any overpayment toward the next monthly installment(s) of Rent due from Tenant or otherwise pay to Tenant the overpayment within thirty (30) days of delivery of the Actual Statement. Prior to the expiration or sooner termination of the Term and Landlord's acceptance of Tenant's surrender of the Premises, Landlord will have the right to estimate the actual Insurance Costs and Taxes for the then current calendar year and to collect from Tenant prior to Tenant's surrender of the Premises, any excess of such actual Operating Expenses over the amount of such corresponding costs actually paid by Tenant in such calendar year.

c. **Audit**. Within one hundred eighty (180) months after receiving Landlord's Actual Statement, Tenant may, upon advance written notice to Landlord and during reasonable business hours, cause an audit of Landlord's books and records with respect to the applicable calendar year to determine the accuracy of Landlord's Actual Statement. Landlord shall make all pertinent records available for inspection that are reasonably necessary for Tenant to conduct its review. If any records are maintained at a location other than the office of the Building, Tenant may either inspect the records at such other location or pay for the reasonable cost of copying and shipping the records. If Tenant retains an agent, at Tenant's sole cost and expense, to review Landlord's records, the agent shall be an independent accountant of national standing which is reasonably acceptable to Landlord, is not compensated on a contingency basis; provided, however, that the foregoing shall not be deemed to limit Tenant's right to have its employees

conduct an audit pursuant to this Section 1.16(c). Within ninety (90) days after the records are made available to Tenant, Tenant shall have the right to give Landlord written notice (an "Objection Notice") stating in reasonable detail any objection to the Actual Statement of Operating Expenses for that year. If Tenant provides Landlord with a timely Objection Notice, Landlord and Tenant shall work together in good faith to resolve any issues raised in Tenant's Objection Notice. If Tenant fails to provide Landlord with a timely Objection Notice, Landlord's Actual Statement shall be deemed final and binding, and Tenant shall have no further right to audit or object to such statement. If Tenant reasonably determines based on its audit that Operating Expenses for the applicable calendar year are less than reported, Landlord shall provide Tenant with a refund in the amount of the overpayment by Tenant within thirty (30) days. Likewise, if Tenant reasonably determines based on its audit that Operating Expenses for the calendar year are greater than reported, Tenant shall pay Landlord the amount of any underpayment within thirty (30) days. The records obtained by Tenant shall be treated as confidential. In no event shall Tenant be permitted to examine Landlord's records or to dispute any statement of Operating Expenses unless Tenant has paid and continues to pay all Rent when due. Notwithstanding anything to the contrary contained in this Section 1.16(c), if it is determined based on Tenant's audit that the amount of Operating Expenses were overstated by more than five percent (5%), then Landlord shall pay Tenant's reasonable out-of-pocket cost for such audit not to exceed $5,000.00.

1.17 **Utilities and Services, and Additional Maintenance Obligations**.

a. **Utilities and Services**. As used in this Lease, "**Utilities Costs**" shall mean all actual charges for utilities for the Premises of any kind, including but not limited to water, sewer and electricity, telecommunications and cable service, and the costs of heating, ventilating and air conditioning and other utilities as well as related fees, assessments and surcharges. Tenant shall contract directly for all utilities services for the Premises and shall pay all Utilities Costs directly to the various utility service providers providing such utility services to the Premises.

b. **Maintenance/Janitorial/Service Contracts**. Tenant shall, at its sole cost and expense, enter into maintenance/service contracts to perform landscaping, roof-cleaning and regularly scheduled preventative maintenance and repair of all hot water, heating and air conditioning systems and equipment ("**HVAC**") within the Premises, or which serve the Premises exclusively, including, without limitation, any rooftop package, HVAC units, distribution lines and internal venting systems. With respect to the HVAC servicing the Office Portions of the Building (as hereinafter defined), such repair and maintenance shall at a minimum conform to the recommendations of the contractor providing the maintenance/service contract for such HVAC. All cleaning and janitorial services, including regular removal of trash and debris, for the Premises shall be performed and obtained, at Tenant's sole cost and expense, exclusively by or through Tenant or Tenant's janitorial contractors. The maintenance contractors for any Operating Systems and any janitorial contractors and the contracts for same must be approved in writing by Landlord in advance, which approval shall not be unreasonably withheld, conditioned or delayed. Notwithstanding the foregoing, Tenant shall have the right, in its sole discretion, to select the contractors for any systems, equipment and/or services related to any portion of the Building other than the office and restroom portions thereof (the "**Office Portions of the Building**") (including, without limitation, any such systems, equipment and/or services related to Tenant's lab, manufacturing and/or R&D operations ("**Tenant's GMP Operations**")). All maintenance/service contracts for anything not related to Tenant's GMP Operations shall, to the extent applicable, include all services recommended by the equipment manufacturer within the operation/maintenance manual, and shall become effective (and a copy thereof delivered to Landlord) within thirty (30) days following the date Tenant takes possession of the Premises. Landlord reserves the right, upon notice to Tenant, to procure and maintain any or all of such service contracts, and if Landlord so elects, Tenant shall reimburse Landlord, as Additional Rent, upon demand, for the cost therefor. Tenant agrees to reasonably cooperate with Landlord to the extent required by Landlord to comply with California Public Resources Code Section 25402.10 including, without limitation, providing or consenting to any utility company providing Tenant's energy consumption information for the Premises to Landlord. Additionally, Tenant hereby consents to any applicable utility company providing utility consumption information for the Premises to Landlord, and if requested, shall promptly sign any documentation reasonably requested by the utility company to evidence such consent.

c. **Tenant's Additional Repair Obligations**. Except for Landlord's obligations specifically set forth elsewhere in this Lease and in Section 8.1 below, Tenant shall at all times and at Tenant's sole cost and expense, keep, maintain, clean, repair, renovate, retrofit, replace and preserve the Premises and all parts thereof, structural and non-structural, including, without limitation, utility meters, plumbing, pipes and conduits, all heating, ventilating and air conditioning systems located within the Premises, all windows, restrooms, ceilings, interior walls, roof, skylights, interior and demising walls, doors, electrical and lighting equipment, sprinkler systems, parking areas, driveways, walkways, parking lots, loading dock areas and doors, rail spur areas, fences, signs, lawns and landscaping, if any, any Tenant Improvements, Alterations or other alterations, additions and other property and/or fixtures located within and upon the Premises in good condition and repair, reasonable wear and tear excepted. Tenant's repair and maintenance obligations shall include, but not be limited to, slurry coating the parking areas as reasonably necessary; parking area and driveway sweeping and repairing; and responsibility for painting. Except for Landlord's obligations specifically set forth elsewhere in this Lease and in Section 8.1 above,

and subject to the last sentence of Section 8.2, Tenant shall at all times during the Term make all non-structural changes, repairs and improvements to the Premises of every kind and nature, whether ordinary or extraordinary, foreseen or unforeseen, which may be required by any Laws or for the safety of the Premises. Such maintenance and repairs shall be performed with due diligence, lien-free and in a good and workmanlike manner, by licensed contractor(s) which are selected by Tenant (and, with respect to any contractors performing work to the Operating Systems and/or in the Office Portions of the Building, approved by Landlord, which approval Landlord shall not unreasonably withhold or delay, provided, Landlord reserves the right to require Tenant to utilize Landlord's preferred contractors, subcontractors and vendors for any such contractors). Except for Landlord's obligations specifically set forth elsewhere in this Lease (including Section 8.1), Landlord has no obligation whatsoever to alter, remodel, improve, repair, renovate, retrofit, replace, redecorate or paint all or any part of the Premises. Notwithstanding the foregoing or anything to the contrary contained herein, Tenant shall have the right to select contractors for purposes of maintenance and repair of any equipment and/or systems related to Tenant's GMP Operations, without the requirement to obtain Landlord's prior approval.

1.18 **Additional Hazardous Materials Requirements.** In addition to Tenant's obligations under Article 10 of the Standard Provisions, Tenant shall comply with the following provisions with respect to Hazardous Materials (as that term is defined in Article 10):

a. **Environmental Questionnaire; Disclosure**. Prior to the execution of this Lease, Tenant shall complete, execute and deliver to Landlord an Environmental Questionnaire and Disclosure Statement (the "**Environmental Questionnaire**") in the form of Exhibit D, and Tenant shall certify to Landlord all information contained in the Environmental Questionnaire as true and correct to the best of Tenant's knowledge and belief. The completed Environmental Questionnaire shall be deemed incorporated into this Lease for all purposes, and Landlord shall be entitled to rely fully on the information contained therein. On each anniversary of the Commencement Date (each such date is hereinafter referred to as a "**Disclosure Date**"), until and including the first Disclosure Date occurring after the expiration or sooner termination of this Lease, Tenant shall disclose to Landlord in writing the names and amounts of all Hazardous Materials, or any combination thereof, that were stored, generated, used or disposed of on, under or about the Premises for the twelve (12) month period prior to each Disclosure Date, and that Tenant intends to store, generate, use or dispose of on, under or about the Premises through the next Disclosure Date. At Landlord's request, Tenant's disclosure obligations under this Section 1.18 shall include a requirement that Tenant update, execute and deliver to Landlord the Environmental Questionnaire; provided, however, Tenant shall not be required to update the Environmental Questionnaire more than once per year unless an environmental Default has occurred during the immediately preceding eighteen (18) month period. In addition to the foregoing, Tenant shall promptly notify Landlord of, and shall promptly provide Landlord with true, correct, complete and legible copies of, all of the following environmental items relating to the Premises: reports filed pursuant to any self-reporting requirements; reports filed pursuant to any Environmental Laws or this Lease; all permit applications, permits, monitoring reports, workplace exposure and community exposure warnings or notices, and all other reports, disclosures, plans or documents (excluding those that may be characterized as confidential) relating to water discharges, air pollution, underground storage tanks or Hazardous Materials; all orders, reports, notices, listings and correspondence (excluding those that may be considered confidential, provided Tenant shall remain liable to address any such confidential Hazardous Materials matters in accordance with this Section 1.18 and Article 10) of or concerning the release, investigation, compliance, clean up, remedial and corrective actions, and abatement of Hazardous Materials whether or not required by Environmental Laws; and all complaints, pleadings and other legal documents filed against Tenant related to Tenant's use, handling, storage or disposal of Hazardous Materials. Tenant may submit an updated Environmental Questionnaire to Landlord from time to time, which updated Environmental Questionnaire shall be subject to Landlord's approval (which approval shall not be unreasonably withheld, conditioned or delayed).

b. **Inspection; Compliance**. Landlord and Landlord Parties shall have the right, but not the obligation, at its sole cost and expense, to inspect, investigate, sample and/or monitor the Premises, including any air, soil, water, groundwater or other sampling, and any other testing, digging, drilling or analyses, at any time to determine whether Tenant is complying with the terms of this Section 1.18, and in connection therewith, Tenant shall, subject to the Access Conditions (as defined in Article 24 below), provide Landlord with access to all relevant facilities, records and personnel. If Tenant is in default of any of the provisions of this Section 1.18 beyond applicable notice and cure periods, or in the event of a release of any Hazardous Materials on, under, from or about the Premises, Landlord and Landlord Parties shall have the right, but not the obligation, without limitation on any of Landlord's other rights and remedies under this Lease but subject to the Access Conditions (as defined in Article 24), to enter upon the Premises and to discharge Tenant's obligations under this Section 1.18 at Tenant's expense, including without limitation the taking of emergency or long term remedial action. Landlord and Landlord Parties shall use all reasonable efforts to minimize interference with Tenant's business. In addition, Landlord, at Landlord's sole cost and expense, shall have the right, but not the obligation, to join and participate in any legal proceedings or actions initiated in connection with any claims or causes of action arising out of the storage, generation, use or disposal by Tenant or Tenant's Parties of Hazardous Materials on, under, from or about the Premises. Landlord agrees that if any testing proves that the Tenant or Tenant's Parties have no responsibility for the presence of said Hazardous Materials, Tenant shall not be liable for any costs or expenses in connection with such inspection, testing and monitoring.

c. **Tenant Obligations**. If the presence of any Hazardous Materials on, under or about the Premises caused by Tenant or Tenant's Parties results in (i) injury to any person, (ii) injury to or contamination of the Premises, or (iii) injury to or contamination of any real or personal property wherever situated, Tenant, at its sole cost and expense, shall, to the extent required by applicable Environmental Law, promptly take all actions necessary to return the Premises to the condition existing prior to the introduction of such Hazardous Materials to the Premises and to remedy or repair any such injury or contamination. Without limiting any other rights or remedies of Landlord under this Lease, Tenant shall pay the cost of any cleanup work performed on, under or about the Premises as required by this Lease or any Environmental Laws in connection with the removal, disposal, neutralization or other treatment of such Hazardous Materials caused by Tenant or Tenant's Parties. If Tenant or Tenant's Parties caused the release of any Hazardous Materials on, under, from or about the Premises in violation of Environmental Laws, then Landlord may require Tenant, at Tenant's sole cost and expense, to conduct monitoring activities on or about the Premises reasonably satisfactory to Landlord concerning such release of Hazardous Materials on, under, from or about the Premises. Notwithstanding anything to the contrary contained in the foregoing, Tenant shall not, without Landlord's prior reasonable written consent, take any remedial action in response to the presence of any Hazardous Materials on, under or about the Premises, or enter into any settlement agreement, consent decree or other compromise with any governmental agency with respect to any Hazardous Materials claims; provided, however, Landlord's prior written consent shall not be necessary in the event that the presence of Hazardous Materials on, under or about the Premises (i) poses an immediate threat to the health, safety or welfare of any individual, or (ii) is of such a nature that an immediate remedial response is necessary and it is not possible to obtain Landlord's consent before taking such action. Tenant's failure to timely comply with this Section 1.18 shall constitute a default under this Lease (subject to the provisions of Section 22.1 below). Landlord and Tenant specifically agree that Tenant shall not be responsible or liable to Landlord or any Landlord Parties for any of Hazardous Materials which are (a) released or brought in, on, under or about the Property by Landlord or Landlord Parties or by any non-Tenant Party and (b) existing in, on, under or about the Premises as of the Effective Date.

d. **Tenant's Responsibility at Conclusion of Lease**. Promptly upon the expiration or sooner termination of this Lease, Tenant shall represent to Landlord in writing that, to the best of Tenant's knowledge, no Hazardous Materials exist on, under or about the Premises as a result of any acts or (where action is required by Tenant under this Lease) omissions of Tenant or its agents, employees or contractors, other than as specifically identified to Landlord by Tenant in writing. If Tenant discloses the existence of any such Hazardous Materials on, under or about the Premises or if Landlord at any time discovers that Tenant or Tenant's Parties caused or permitted the release of any such Hazardous Materials on, under, from or about the Premises in violation of applicable Environmental Laws, Tenant shall, at Landlord's request, immediately prepare and submit to Landlord within thirty (30) days after such request a comprehensive plan, subject to Landlord's approval, specifying the actions to be taken by Tenant to return the Premises to the condition existing prior to the introduction of such Hazardous Materials. Upon Landlord's approval of such clean-up plan, Tenant shall, at Tenant's sole cost and expense, without limitation on any rights and remedies of Landlord under this Lease or at law or in equity, immediately implement such plan and proceed to clean up such Hazardous Materials in accordance with all Environmental Laws and as required by such plan and this Lease. For purposes of clarification and notwithstanding anything to the contrary contained herein, in no event shall Tenant's obligations under this Section 1.18(d) or elsewhere in this Lease require Tenant to remove, remediate or encapsulate any Hazardous Materials from the Premises (i) which existed in, on or under the Premises, prior to the Commencement Date and (ii) which were not introduced by Tenant or Tenant's Parties.

e. **Landlord Obligations**. Landlord hereby represents to Tenant, to Landlord's actual knowledge, as of the Effective Date that there are no Hazardous Materials existing on, in, under or about the Premises ("**Landlord's Hazardous Materials Warranty**") in excess of levels that require remediation under Environmental Laws. In the event (i) of any breach of Landlord's Hazardous Materials Warranty and/or (ii) any Hazardous Materials (either (x) the introduction of which was not caused by Tenant or any of Tenant's Parties and was caused by Landlord or any Landlord Parties or (y) that existed on, in, under or about the Premises prior to the date Tenant first takes possession of the Premises) are discovered on, in, under or about the Premises in excess of levels that require remediation and/or removal under Environmental Laws (either (i) or (ii), a "**Landlord HazMat Event**"), then (a) Landlord, at its sole cost and expense, shall remove and/or remediate the applicable Hazardous Materials in compliance with and to the extent required under applicable Environmental Laws, and (b) Landlord shall indemnify, protect, defend and hold harmless Tenant and Tenant's Parties from and against any and all claims, damages, judgments, suits, causes of action, liabilities, penalties, fines, expenses and costs (including, without limitation, attorneys' fees, consultant fees and expert fees and court costs) which arise or result from such Landlord HazMat Event. Any costs incurred by Landlord in connection with this paragraph (e) shall be specifically excluded from Operating Expenses.

f. The provisions of this Section 1.18 will survive the expiration or earlier termination of this Lease.

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STANDARD LEASE PROVISIONS

ARTICLE 2 - LEASE

2.1 **Lease Elements; Definitions; Exhibits.** The Lease is comprised of the Lease Summary and Property Specific Provisions (the "**Summary**"), these Standard Lease Provisions ("**Standard Provisions**") and all exhibits, and riders attached hereto (collectively, "**Exhibits**"), all of which are incorporated together as part of one and the same instrument. All references in any such documents and instruments to "Lease" means the Summary, these Standard Provisions and all Exhibits attached hereto. All terms used in this Lease shall have the meanings ascribed to such terms in the Summary, these Standard Provisions and any Exhibits. To the extent of any inconsistency between the terms and conditions of the Summary, these Standard Provisions, or any Exhibits attached hereto, the Summary and any Exhibits attached hereto shall control over these Standard Provisions.

ARTICLE 3 - PREMISES

3.1 **Lease of Premises**. Landlord hereby leases to Tenant, and Tenant hereby leases from Landlord, the Premises, upon and subject to, the terms, covenants and conditions of this Lease. Each party covenants and agrees, as a material part of the consideration for this Lease, to keep and perform their respective obligations under this Lease.

ARTICLE 4- TERM AND POSSESSION

4.1 **Term; Notice of Lease Term Dates**. The Term shall be for the period designated in the Summary commencing on the Commencement Date and ending on the Expiration Date, unless the Term is sooner terminated or extended as provided in this Lease. Within ten (10) days after either party's written request, both parties shall execute a written confirmation of the Commencement Date and Expiration Date of the Term in the form of the Notice of Lease Term Dates attached hereto as Exhibit B. The Notice of Lease Term Dates shall be binding upon both parties unless the other party reasonably objects thereto in writing within such ten (10) day period.

4.2 **Possession**. Landlord shall deliver possession of the Premises to Tenant in its present AS-IS condition, subject to the provisions of Section 4.3 and 4.4 below.

4.3 **Early Access**. So long as Landlord has received from Tenant the Monthly Base Rent and Additional Rent for month 9 of the Term pursuant to Section 5.1 of this Lease, along with certificates reasonably satisfactory to Landlord evidencing the insurance required to be carried by Tenant under this Lease, and, as applicable, the Security Deposit and/or letter of credit required of Tenant, Tenant may have access to the Premises effective as of the Effective Date through to the Commencement Date (the "**Early Access Period**"). Tenant's access to the Premises during the Early Access Period shall be subject to all terms and conditions of this Lease, except that Tenant shall not be obligated to pay Rent or Operating Expenses during the Early Access Period until the Commencement Date and such obligations commence as provided in this Lease. Tenant agrees to provide Landlord with prior notice of any such intended early access.

4.4 **Condition of Premises**. Landlord shall deliver the Premises to Tenant (i) in broom-clean condition and free of debris, (ii) free of tenants or other occupants, and (iii) with the existing Building standard plumbing and lighting systems (but exclusive of all HVAC units and systems, the "**Operating Systems**") in good operating condition for the AS-IS configuration of the Premises; provided, however, notwithstanding the foregoing, Tenant shall be responsible for repairs to the roof, the HVAC system and exterior ADA compliance issues on the terms provided in subparagraphs a., b. and c below, all of which shall not be part of Landlord's delivery obligation or covered by the foregoing Landlord warranty. If any of such Operating Systems or elements should malfunction or fail within the Warranty Period (defined below), as Tenant's sole remedy for Landlord's breach of this warranty, Landlord shall, as Landlord's sole obligation, promptly after receipt of written notice from Tenant setting forth with specificity the nature and extent of such non-compliance, malfunction or failure, repair or replace (as the case may be) same at Landlord's expense to the extent necessary to put the same in good operating condition; provided, however, Landlord shall have no liability hereunder for repairs or replacements necessitated by the acts or (where action by Tenant is required hereunder) omissions of Tenant and/or any of Tenant's Parties other than reasonable wear and tear. The "**Warranty Period**" as to all Operating Systems shall be the period commencing upon delivery of the Premises to Tenant, including any Early Access Period under Section 4.3 above, and ending on the date twelve (12) months after the Rent Commencement Date. If Tenant does not give Landlord the required notice within said Warranty Period, correction of any such non-compliance, malfunction or failure shall be the obligation of Tenant at Tenant's sole cost and expense; provided, however, that the foregoing shall not abrogate any of Landlord's other obligations under this Lease.

a. **Roof Work**. On or before [***], Tenant shall replace the roof membrane of the Building [***] (the "**Roof Work**"), at Tenant's sole cost and expense, provided Landlord shall provide Tenant with an additional allowance in the amount of $[***] (the "**Roof Allowance**") which Tenant may apply towards cost of such Roof Work. Tenant shall provide Landlord with written notice of completion of the Roof Work promptly upon completion, together with a copy of the warranty for the new roof provided by the roofing contractor, [***].

b. **Exterior ADA Work**. [***] ([***], the "**Exterior ADA Work**"). If in connection with obtaining permits for any Tenant Improvements or during the course of completing any Tenant Improvements prior to [***], Tenant is advised by any governmental authority that any specific Exterior ADA Work [***] must be completed as a condition to receipt of a permit to commence any Tenant Improvements or governmental approval as to completion of any Tenant Improvements, Tenant shall promptly notify Landlord in writing of such requirement and the specific elements of the Exterior ADA Work that must be completed as a condition to such permit or final sign-off as to such Tenant Improvements and the schedule and estimated cost for such specified portion of the Exterior ADA Work. Unless Landlord provides written notice to Tenant within [***] days of Landlord's receipt of any such notice from Tenant of Landlord's objection to the scope or cost of such specified Exterior ADA Work, Tenant may perform such specified portions of the Exterior ADA Work and Landlord shall reimburse Tenant for any actual, reasonable and documented costs incurred by Tenant in connection with the same within thirty (30) days after Tenant's written request therefor up to a maximum amount of $[***].

c. **HVAC Work**. On or before December 31, 2020, Tenant will cause the HVAC systems serving the office areas of the Building shown on Schedule 4.4.1 attached hereto to be repaired or replaced in their existing locations so they are in good operating condition for the AS-IS configuration of the Premises, subject to Tenant's improvement plans as to use of the existing HVAC units and any resulting changes to the HVAC distribution required for Tenant's desired configuration of the Premises (which shall be Tenant's obligation and cost) ("**HVAC Work**"), at Tenant's sole cost and expense, provided Landlord shall provide Tenant with an additional allowance in the amount of $[***] (the "**HVAC Allowance**") which Tenant may apply towards cost of such HVAC Work. Tenant shall provide Landlord with written notice of completion of the HVAC Work promptly upon completion, together with a copy of the warranty for the new HVAC units provided by the HVAC contractor, [***], whereupon Landlord shall disburse the HVAC Allowance to Tenant.

d. **Interference**. Tenant acknowledges that the Roof Work, the Exterior ADA Work and the HVAC Work may be performed while Tenant is performing Tenant's Work and/or occupying the Premises, and Landlord shall have no liability for any interference with Tenant's Work or occupancy resulting from Tenant performing such work.

Tenant acknowledges that, except as otherwise expressly set forth above in this Section 4.3 or elsewhere in this Lease, (i) neither Landlord nor any agent of Landlord has made any representation or warranty with respect to the Premises, or with respect to the condition and/or suitability thereof for the conduct of Tenant's business, and Tenant shall accept the Premises in its current AS-IS condition subject only to vacation of the Premises by the existing tenant, and (ii) the acceptance of possession of the Premises by Tenant shall establish that the Premises were at such time complete and in good, sanitary and satisfactory condition and repair with all work required to be performed by Landlord, if any, completed and without any obligation on Landlord's part to make any further alterations, upgrades or improvements thereto. Pursuant to Section 1938 of the California Civil Code, Landlord hereby advises Tenant that as of the date of this Lease, except for the Exterior ADA Report, neither the Premises, nor the Building have undergone inspection by a Certified Access Specialist (CASp). Further, pursuant to Section 1938 of the California Civil Code, Landlord notifies Tenant of the following: "A Certified Access Specialist (CASp) can inspect the Premises and determine whether the Premises comply with all of the applicable construction-related accessibility standards under state law. Although California state law does not require a CASp inspection of the Premises, the commercial property owner or lessor may not prohibit the lessee or tenant from obtaining a CASp inspection of the Premises for the occupancy or potential occupancy of the lessee or tenant, if requested by the lessee or tenant. The parties shall mutually agree on the arrangements for the time and manner of any such CASp inspection, the payment of the costs and fees for the CASp inspection and the cost of making any repairs necessary to correct violations of construction-related accessibility standards within the Premises." Therefore and notwithstanding anything to the contrary contained in this Lease, Landlord and Tenant agree that (a) Tenant may, at its option and at its sole cost, cause a CASp to inspect the Premises and determine whether the Premises complies with all of the applicable construction-related accessibility standards under California law, (b) the parties shall mutually coordinate and reasonably approve of the timing of any such CASp inspection so that Landlord may, at its option, have a representative present during such inspection, and, (c) subject to the last sentence of Section 8.2, and, separate from the treatment of Exterior ADA Work described above, Tenant shall be solely responsible for the cost of any repairs required by Law to correct violations of construction-related accessibility standards within the Premises, any and all such alterations and repairs to be performed in accordance with Article 13 of this Lease provided Tenant shall have no obligation to remove any repairs or alterations made pursuant to a CASp inspection under this Section 4.4.

ARTICLE 5- RENT

5.1 **Monthly Base Rent**. Tenant agrees to pay Landlord, the Monthly Base Rent as designated in the Summary. Monthly Base Rent and recurring monthly charges of Additional Rent (defined below) shall be paid by Tenant in advance on the first day of each and every calendar month ("**Due Date**") during the Term commencing on the Rent Commencement Date, except that the Monthly Base Rent and Additional Rent due for month 9 of the Term shall be paid upon Tenant's execution and delivery of this Lease to Landlord. Monthly Base Rent for any partial month shall be prorated in the proportion that the number of days this Lease is in effect during such month bears to the actual number of days in such month.

5.2 **Additional Rent**. All amounts and charges payable by Tenant under this Lease in addition to Monthly Base Rent, if any, including, without limitation, payments for Operating Expenses, Taxes, Insurance Costs and Utilities Costs to the extent payable by Tenant to Landlord under this Lease shall be considered "**Additional Rent**", and the word "**Rent**" in this Lease shall include Monthly Base Rent and all such Additional Rent unless the context specifically states or clearly implies that only Monthly Base Rent is referenced. Rent shall be paid to Landlord, without any prior notice or demand therefor and without any notice, deduction or offset, in lawful money of the United States of America.

5.3 **Late Charges & Interest Rate**. If Landlord does not receive Rent or any other payment due from Tenant on the Due Date with respect to recurring charges and the due date specified herein with respect to any other charges, Tenant shall pay to Landlord a late charge equal to five percent (5%) of such past due Rent or other payment; provided, however, Landlord agrees to waive the foregoing late charge one time per twelve (12) month period so long as Tenant cures such nonpayment within five (5) days following Landlord's written demand therefor. Tenant agrees that this late charge represents a fair and reasonable estimate of the cost Landlord will incur by reason of Tenant's late payment. Accepting any late charge shall not constitute a waiver by Landlord of Tenant's default with respect to any overdue amount nor prevent Landlord from exercising any other rights or remedies available to Landlord. If any installment of Monthly Base Rent or Additional Rent, or any other amount payable by Tenant hereunder is not received by Landlord by the Due Date with respect to recurring charges and the due date specified herein with respect to any other charges, it shall bear interest at the Interest Rate set forth in the Summary from the Due Date until paid. All interest, and any late charges imposed pursuant to this Section 5.3, shall be considered Additional Rent due from Tenant to Landlord under the terms of this Lease.

ARTICLE 6 - LETTER OF CREDIT

6.1 **General Provisions**. Concurrently with Tenant's execution of this Lease, Tenant shall deliver to Landlord, as additional collateral for the full performance by Tenant of all of its obligations under this Lease and for all losses and damages Landlord may suffer as a result of any default by Tenant under this Lease, including, but not limited to, any post lease termination damages under section 1951.2 of the California Civil Code, a standby, unconditional, irrevocable, transferable letter of credit (the "**Letter of Credit**") in the form of Exhibit G attached hereto and containing the terms required herein, in the face amount of $[***] (the "**Letter of Credit Amount**"), naming Landlord as beneficiary, issued by a financial institution acceptable to Landlord in Landlord's reasonable discretion (Landlord hereby approving [***] as such an acceptable financial institution), permitting multiple and partial draws thereon, and otherwise in form acceptable to Landlord in its reasonable discretion. Tenant shall cause the Letter of Credit to be continuously maintained in effect (whether through replacement, renewal or extension) in the Letter of Credit Amount through the date (the "**Final LC Expiration Date**") that is [***] after the scheduled expiration date of the Term or any Option Term of this Lease. If the Letter of Credit held by Landlord expires earlier than the Final LC Expiration Date (whether by reason of a stated expiration date or a notice of termination or non-renewal given by the issuing bank), Tenant shall deliver a new Letter of Credit or certificate of renewal or extension to Landlord not later than [***] prior to the expiration date of the Letter of Credit then held by Landlord. Any renewal or replacement Letter of Credit shall comply with all of the provisions of this Article 6, shall be irrevocable, transferable and shall remain in effect (or be automatically renewable) through the Final LC Expiration Date upon the same terms as the expiring Letter of Credit or such other terms as may be acceptable to Landlord in its sole discretion.

6.2 **Drawings under Letter of Credit**. Landlord shall have the immediate right to draw upon the Letter of Credit, in whole or in part, at any time and from time to time: (i) If a Default (as defined in Section 22.1 below) occurs; or (ii) If the Letter of Credit held by Landlord expires (or is set to expire) earlier than the Final LC Expiration Date (whether by reason of a stated expiration date or a notice of termination or non-renewal given by the issuing bank), and Tenant fails to deliver to Landlord, at least [***] prior to the expiration date of the Letter of Credit then held by Landlord, a renewal or substitute Letter of Credit that is in effect and that complies with the provisions of this Article 6. No condition or term of this Lease shall be deemed to render the Letter of Credit conditional to justify the issuer of the Letter of Credit in failing to honor a drawing upon such Letter of Credit in a timely manner. Tenant hereby acknowledges and agrees that Landlord is entering into this Lease in material reliance upon the ability of Landlord to draw upon the Letter of Credit upon the occurrence of any event of default by Tenant under this Lease.

6.3 **Use of Proceeds by Landlord**. The proceeds of the Letter of Credit shall constitute Landlord's sole and separate property (and not Tenant's property or the property of Tenant's bankruptcy estate) and Landlord may immediately upon any draw (and without notice to Tenant) apply or offset the proceeds of the Letter of Credit: (i) against any rent payable by Tenant under this Lease that is not paid when due; (ii) against all losses and damages that Landlord has suffered or that Landlord reasonably estimates that it may suffer as a result of any default by Tenant under this Lease, including any damages arising under section 1951.2 of the California Civil Code following termination of the Lease; (iii) against any costs incurred by Landlord in connection with this Lease (including attorneys' fees); and (iv) against any other amount that Landlord may spend or become obligated to spend by reason of Tenant's default (provided that Landlord may not draw upon the Letter of Credit as aforesaid until after a Default has occurred, as set forth in Section 6.2 above). Provided Tenant has performed all of its obligations under this Lease, Landlord agrees to pay to Tenant within thirty (30) days after the Final LC Expiration Date the amount of any proceeds of the Letter of Credit received by Landlord and not applied as allowed above; provided, that if prior to the Final LC Expiration Date a voluntary petition is filed by Tenant, or an involuntary petition is filed against Tenant by any of Tenant's creditors, under the Federal Bankruptcy Code, then Landlord shall not be obligated to make such payment in the amount of the unused Letter of Credit proceeds until either all preference issues relating to payments under this Lease have been resolved in such bankruptcy or reorganization case or such bankruptcy or reorganization case has been dismissed, in each case pursuant to a final court order not subject to appeal or any stay pending appeal.

6.4 **Additional Covenants of Tenant**. If, as result of any application or use by Landlord of all or any part of the Letter of Credit, the amount of the Letter of Credit shall be less than the Letter of Credit Amount, Tenant shall, within 15 days thereafter, provide Landlord with additional letter(s) of credit in an amount equal to the deficiency (or a replacement letter of credit in the total Letter of Credit Amount), and any such additional (or replacement) letter of credit shall comply with all of the provisions of this Article 6, and if Tenant fails to comply with the foregoing, notwithstanding anything to the contrary contained in this Lease, the same shall, at Landlord's election, constitute an event of default by Tenant. Tenant further covenants and warrants that it will neither assign nor encumber the Letter of Credit or any part thereof and that neither Landlord nor its successors or assigns will be bound by any such assignment, encumbrance, attempted assignment or attempted encumbrance.

6.5 **Transfer of Letter of Credit**. Landlord may, at any time and without notice to Tenant and without first obtaining Tenant's consent thereto, transfer all or any portion of its interest in and to the Letter of Credit to another party, person or entity, including Landlord's mortgagee and/or to have the Letter of Credit reissued in the name of Landlord's mortgagee. If Landlord transfers its interest in the Building and transfers the Letter of Credit (or any proceeds thereof then held by Landlord) in whole or in part to the transferee, Landlord shall, without any further agreement between the parties hereto, thereupon be released by Tenant from all liability therefor. The provisions hereof shall apply to every transfer or assignment of all or any part of the Letter of Credit to a new landlord. In connection with any such transfer of the Letter of Credit by Landlord, Tenant shall, at Tenant's sole cost and expense, execute and submit to the issuer of the Letter of Credit such applications, documents and instruments as may be necessary to effectuate such transfer. Tenant shall be responsible for paying the issuer's transfer and processing fees in connection with any transfer of the Letter of Credit and, if Landlord advances any such fees (without having any obligation to do so), Tenant shall reimburse Landlord for any such transfer or processing fees within ten days after Landlord's written request therefor.

6.6 **Nature of Letter of Credit**. Tenant hereby waives [***] and all other provisions of Law, now or hereafter in effect, which (A) [***], and/or (B) [***], it being agreed that Landlord may, in addition, [***].

6.7 **Reduction to Letter of Credit**. Landlord agrees that Tenant shall have the right to reduce the Letter of Credit Amount by [***]. Such reduction in the Letter of Credit Amount shall be accomplished, at Tenant's option, by either providing (a) a substitute Letter of Credit in the reduced amount or (b) an amendment to the Letter of Credit reducing it to the reduced amount. If during [***], Tenant shall, upon Landlord's request, restore the Letter of Credit Amount to its full original amount, subject to reduction again as provided herein if Tenant shall restore its cash balance to [***] provided Tenant is not in Default at such time beyond applicable notice and cure periods under this Lease.

ARTICLE 7- OPERATING EXPENSES/UTILITIES/SERVICES

7.1 **Utilities and Services**. Utilities and services to the Premises are described in the Summary and are paid directly by Tenant.

7.2 **Taxes.** As used in this Lease, the term "**Taxes**" means: All real property taxes and assessments, possessory interest taxes, sales taxes, personal property taxes, business or license taxes or fees, gross receipts taxes, license or use fees, excises, transit charges, and other impositions of any kind (including fees "in-lieu" or in substitution of any such tax or assessment) which are now or hereafter assessed, levied, charged or imposed by any public authority upon the Premises or any portion thereof, its

operations or the Rent derived therefrom (or any portion or component thereof, or the ownership, operation, or transfer thereof), and any and all costs and expenses (including, without limitation, reasonable attorneys' fees) reasonably incurred in attempting to protest, reduce or minimize the same. Taxes shall not include (i) inheritance or estate taxes imposed upon or assessed against the interest of Landlord, gift taxes, excess profit taxes, franchise taxes, or similar taxes on Landlord's business or any other taxes computed upon the basis of the net income of Landlord, or transfer taxes. If it shall not be lawful for Tenant to reimburse Landlord for any such Taxes, the Monthly Base Rent payable to Landlord under this Lease shall be revised to net Landlord the same net rent after imposition of any such Taxes by Landlord as would have been payable to Landlord prior to the payment of any such Taxes. Tenant shall pay for or contribute to Taxes as provided in the Summary. Notwithstanding anything herein to the contrary, Tenant shall be liable for all taxes levied or assessed against personal property, furniture, fixtures, above-standard Tenant Improvements and alterations, additions or improvements placed by or for Tenant in the Premises. Furthermore, Tenant shall pay prior to delinquency any (i) rent tax or sales tax, service tax, transfer tax or value added tax, or any other applicable tax on the rent or services provided herein or otherwise respecting this Lease, (ii) taxes assessed upon or with respect to the possession, leasing, operation, management, maintenance, alteration, repair, use or occupancy by Tenant of the Premises or any portion thereof; or (iii) taxes assessed upon this transaction or any document to which Tenant is a party creating or transferring an interest or an estate in the Premises. Upon Tenant's written request, Landlord shall provide a copy of the applicable tax bill to Tenant. If Landlord shall receive any tax refund or reimbursement of Taxes or sum in lieu thereof with respect to Taxes attributable to periods occurring during the Term, then out of any balance remaining thereof after deducting Landlord's reasonable expenses in obtaining such refund (unless such expenses had previously been included in Taxes as aforesaid), Landlord shall promptly refund any such amount to and previously paid by Tenant. If any betterment or special assessment shall be payable in installments without interest, whether or not Landlord elects to pay the same over the longest period permitted, Tenant's payments on account of such betterment or special assessment shall be based on the installments payable with respect to each year during the Term as if Landlord had elected to pay the same over the longest period permitted. If Landlord does not contest the amount or validity of Taxes for any tax year in question, Tenant shall have the right to contest the amount or validity of Taxes for any tax year in question by appropriate administrative and legal proceedings brought either in the Tenant's name, Landlord's name or jointly with Landlord, as Tenant may deem appropriate, by counsel selected and engaged by Tenant; provided, however, Tenant shall notify Landlord prior to initiating any such tax contest and Landlord (rather than Tenant) may contest such Taxes in Landlord's name and with counsel selected by Landlord so long as Landlord promptly and diligently pursues such tax contest to completion. Landlord and Tenant agree to provide reasonable assistance in any such contest including providing the other with a copy of all assessments and tax bills promptly and within any appeal period, and if Tenant shall pursue such tax contest, Landlord shall execute and deliver to the Tenant whatever documents may be necessary or proper to permit the Tenant to contest Taxes and/or the assessment or which may be necessary to secure payments of any refund which may result from any such proceedings. Any refund resulting from a proceeding brought either by Tenant or Landlord or by them jointly shall be applied first to reimburse the party or parties who brought the proceeding for the costs incurred with the proceeding, and then to reimburse Tenant for the difference between the amount Tenant paid for Taxes for each fiscal tax year involved in the proceeding and the amount Tenant would have been required to pay if the Taxes had been assessed in accordance with the decision rendered in the proceeding, together with interest on the amount of such difference at the annual rate allowed by the court on the overpayment of the Taxes. Any remaining balance shall be paid to Landlord.

7.3 **Insurance Costs.** As used in this Lease, "**Insurance Costs**" means the cost of insurance obtained by Landlord pursuant to Article 15 including any deductibles that are permitted to be included in Insurance Costs pursuant to Article 15 below. Tenant shall pay for or contribute to Insurance Costs as provided in the Summary.

7.4 **Property Management Fee**. Tenant shall pay the Management Fee as provided in Section 1.16 of the Summary.

7.5 **Interruption of Utilities**. Landlord shall have no liability to Tenant for any interruption in utilities or services to be provided to the Premises when such failure is caused by all or any of the following: (a) accident, breakage or repairs; (b) strikes, lockouts or other labor disturbances or labor disputes of any such character; (c) governmental regulation, moratorium or other governmental action; (d) inability, despite the exercise of reasonable diligence, to obtain electricity, water or fuel; (e) service interruptions or any other unavailability of utilities resulting from causes beyond Landlord's control including without limitation, any electrical power "brown-out" or "black-out"; or (f) any other cause beyond Landlord's reasonable control. In addition, in the event of any such interruption in utilities or services, Tenant shall not be entitled to any abatement or reduction of Rent (except as expressly provided in Articles 17 and 18 if such failure is a result of any casualty damage or taking described therein), no eviction of Tenant shall result, and Tenant shall not be relieved from the performance of any covenant or agreement in this Lease. Tenant hereby waives the provisions of any applicable existing or future Law, ordinance or governmental regulation permitting the termination of this Lease due to an interruption, failure or inability to provide any services (including, without limitation, to the extent the Premises are located in California, the provisions of California Civil Code Section 1932(1)). In no event shall Landlord be liable for any

interruption or failure in the supply of any such utility or other services to Tenant. Except as provided in Section 7.6 below, in no event shall any Rent owed Landlord under this Lease be abated by reason of the failure to furnish, delay in furnishing, unavailability or diminution in quality or quantity of any such utility or other services or interference with Tenant's business operations as a result of any such occurrence; nor shall any such occurrence constitute an actual or constructive eviction of Tenant or a breach of an implied warranty by Landlord.

7.6 **Abatement**. Notwithstanding anything to the contrary contained in this Lease, if Tenant's use of all or any material part of the Premises is materially impaired due to an interruption of utility or mechanical services to the Premises solely as a result of the act or omission or negligence of Landlord (and expressly excluding any service provider initiated "brown-out," "black-out," or other similar interruption in service) for two (2) consecutive business days (such two (2) consecutive business day period to be subject to extension for Force Majeure) (such period, as so extended, is referred to herein as the "**Eligibility Period**"), then Tenant shall be entitled to an equitable abatement of Monthly Base Rent and additional rent under this Lease based upon the portion of the Premises affected thereby (provided that if the operation of Tenant's business from the remainder of the Premises not affected thereby is not reasonably practicable under the circumstances and Tenant in fact does not operate for business from the remainder of the Premises, all Monthly Base Rent and additional rent under this Lease shall be subject to such abatement) from the expiration of the Eligibility Period until the applicable material impairment is cured; provided, however, that if Landlord is diligently pursuing the repair of such utilities or services and Landlord provides substitute services reasonably suitable (as determined by Tenant in its sole discretion) for Tenant's purposes, such as for example, bringing in portable air-conditioning equipment, then there shall not be any abatement of Rent. The provisions of this Section 7.6 shall not apply in the event of a casualty governed by the provisions of Article 17 below or in the event of a taking or condemnation governed by the provisions of Article 18 below.

ARTICLE 8 - MAINTENANCE AND REPAIR

8.1 **Landlord's Repair Obligations**. Landlord shall, at Landlord's sole cost and expense, keep, maintain, repair and replace, as necessary, the structural elements of the Building (including the foundation and load bearing structural walls of the Building, the roof structure and the parking lot foundation), except for damage to any such structural elements caused by Tenant, which Landlord shall repair at Tenant's cost and expense (subject to the waiver of claims and subrogation set forth in Article 19 below). Except as otherwise expressly provided in this Section 8.1 or elsewhere in this Lease, Landlord shall have no obligation to alter, remodel, improve, repair, renovate, redecorate or paint all or any part of the Premises. Except as otherwise stated in the Summary, Tenant waives the right to make repairs at Landlord's expense under any applicable Laws (including, without limitation, to the extent the Premises are located in California, the provisions of California Civil Code Sections 1941 and 1942 and any successor statutes or laws of a similar nature). All other repair and maintenance of the Premises to be performed by Landlord, if any, shall be as provided in the Summary.

8.2 **Tenant's Repair Obligations**. Except for Landlord's obligations specifically set forth elsewhere in this Lease and in Section 8.1 above, Tenant shall at all times and at Tenant's sole cost and expense, keep, maintain, clean, repair, preserve and replace, as necessary, the Premises and all non-structural parts thereof, interior and exterior, including, without limitation, the Building, non-structural portions of the roof (including roof membrane, skylights, gutters and downspouts), non-structural exterior walls, windows, the surface of all parking areas (including slurry coat and striping), all drive aisles, driveways, sidewalks, truck docks and doors and loading areas and equipment, all landscaping and exterior lighting and all electrical and water lines serving same, all Tenant Improvements, Alterations, and all furniture, fixtures and equipment, including, without limitation, all computer, telephone and data cabling and equipment, Tenant's signs, if any, door locks, closing devices, security devices, interior of windows, window sashes, casements and frames, floors and floor coverings, shelving, kitchen, restroom facilities and/or appliances of any kind located within the Premises, if any, custom lighting, and any additions and other property located within the Premises, so as to keep all of the foregoing elements of the Premises in good condition and repair, reasonable wear and tear and casualty damage excepted. Tenant shall replace, at its expense, any and all plate and other glass in and about the Premises which is damaged or broken from any cause whatsoever except due to the negligence or willful misconduct of Landlord, its agents or employees. Such maintenance and repairs shall be performed with due diligence, lien-free and in a good and workmanlike manner, by licensed contractor(s) that are selected by Tenant and approved by Landlord, which approval Landlord shall not unreasonably withhold or delay; provided, however, that Tenant may, at its sole discretion, select the contractors to maintain and/or repair any equipment and/or systems related to Tenant's GMP Operations. All other repair and maintenance of the Premises to be performed by Tenant, if any, shall be as provided in the Summary. If Tenant refuses or neglects to repair and maintain the Self-Help Portions of the Premises (as hereinafter defined) properly as required hereunder, then at any time following ten (10) business days from the date on which Landlord makes a written demand on Tenant to effect such repair and maintenance, Landlord may, subject to the Access Conditions (as defined in Article 24 below), enter upon the Premises and make such repairs and/or maintenance, and upon completion thereof, Tenant agrees to pay to Landlord as Additional Rent, Landlord's costs for making such repairs plus an amount not to exceed ten percent (10%) of such costs for overhead, within thirty (30) days after receipt

from Landlord of a written itemized bill therefor. Any amounts not reimbursed by Tenant within such thirty (30) day period will bear interest at the Interest Rate until paid by Tenant. As used herein, the "**Self-Help Portions of the Premises**" shall mean the exterior of the Building, the exterior of the Property, the Office Portion of the Building and the Operating Systems (but shall specifically exclude, without limitation, any Secure Areas and/or any maintenance and/or repair obligations related to Tenant's GMP Operations). If during the last eighteen (18) months of the Term Tenant reasonably determines that the Premises require any capital improvement to the Premises which are not specific to Tenant's operations and cannot be effectively addressed through continued repair in lieu of capital replacement or improvement and which Tenant reasonably estimates will cost in excess of $[***] and will have a useful life which will extend beyond the then remaining Term (each such capital improvement, a "**Shared Capital Improvement**"), then Landlord shall, within thirty (30) days after Tenant's written demand therefor, obtain construction bids for such work and contract to complete and cause the prompt completion thereafter of such Shared Capital Improvements, in which event Tenant shall reimburse Landlord for the Amortized Portion (as hereinafter defined) all of the costs incurred by Landlord with respect to any such Shared Capital Improvement. As used herein, "**Amortized Portion**" shall mean, with respect to the Shared Capital Improvement in question, the percentage obtained by dividing (i) the number of days remaining in the Term as of the date Landlord makes such Shared Capital Improvement by (ii) the useful life of such Shared Capital Improvement. By way of example, if Landlord completes a Shared Capital Improvement with a five-year useful life one year before the then-scheduled expiration of the Term and Landlord incurs $[***] of expenses in connection with such Shared Capital Improvement, then the Amortized Portion with respect to such expenses would be [***]. Therefore, Tenant would be obligated to reimburse Landlord for $[***] on account of such Shared Capital Improvement within thirty (30) days after Landlord's written demand. Notwithstanding the foregoing or anything to the contrary contained herein, Tenant shall not be required to perform any repairs or alterations to the Premises or the Building in order to comply with any Laws unless such compliance is triggered by (i) Tenant's alterations or improvements to the Premises or (ii) Tenant's particular use of the Premises (i.e., other than for industrial and/or manufacturing use generally), including any such uses related to Tenant's GMP Operations.

8.3 **Tenant's Self-Help Rights**. Notwithstanding Section 8.1 above or any other terms and conditions set forth in this Lease to the contrary, if Tenant provides notice to Landlord of an event or circumstance which requires the action of Landlord under this Lease with respect to the Premises and the repair and/or maintenance of the portions thereof required to be maintained by Landlord under the Lease, and Landlord fails to perform any corrective actions within a reasonable period of time given the nature of the repair, but not to exceed thirty (30) days following receipt of written notice from Tenant as set forth above (except in cases of emergency where Tenant's conduct of Tenant's permitted use is adversely and materially affected, in which case one (1) business day after receipt of such notice or such later period of time as is reasonably necessary to commence such corrective action), Tenant shall be permitted to perform such obligations in the Premises on Landlord's behalf, provided Tenant first delivers to Landlord an additional five (5) days prior written notice indicating that Tenant will be performing such obligations, except in the case of emergency where no additional notice shall be required, and provided Landlord fails to commence to perform its obligation(s) within such additional five (5) day period or thereafter fails to diligently complete performance of such obligations having commenced performance within such five (5) day period, and if such action was required under the provisions of this Lease to be taken by Landlord and was not commenced by Landlord within such five (5) business day period and thereafter diligently pursued to completion, then Tenant shall be entitled to prompt reimbursement by Landlord of Tenant's reasonable costs and expenses in taking such action plus interest thereon at the Interest Rate. Notwithstanding the foregoing, if the nature of the unperformed obligation is such that a bona fide emergency involving an immediate and imminent threat to life, health, property or Tenant's business operations exists, and if the condition in Tenant's reasonable judgment does not permit time for notice to Landlord, Tenant shall be permitted to perform such obligations on Landlord's behalf and Tenant shall be entitled to prompt reimbursement by Landlord of Tenant's reasonable costs and expenses in taking such action. If the obligations to be performed by Tenant will affect the Building's life safety, electrical, plumbing, or sprinkler systems, Tenant shall use only those contractors used by Landlord in the Building for work on such systems and previously identified to Tenant in writing if such contractors are willing and available at commercially reasonably rates or timely perform such work, otherwise Tenant may utilize the services of any other qualified, duly licensed contractor which normally and regularly performs similar work in Comparable Buildings (and provided all requisite permits have been obtained for the desired work), provided however, in an emergency situation, Tenant may use any duly licensed contractor. Any work performed by or on behalf of Tenant shall be performed in a good and workmanlike manner. Landlord agrees to reimburse Tenant within thirty (30) days following receipt from Tenant of a written statement of all actual costs incurred by Tenant in performing such obligations on behalf of Landlord. If Landlord fails to pay such costs to Tenant within such 30-day period, Tenant shall have the right to offset such costs (together with interest on such unpaid amounts from the date originally due at Interest Rate) against the next payment(s) of Monthly Base Rent coming due until Tenant has recovered same in full; provided, however, Tenant may not offset an amount greater than [***] in any month during which Tenant applies such an offset.

ARTICLE 9 - USE

Tenant shall procure, at its sole cost and expense, any and all permits required by applicable Law for Tenant's use and occupancy of the Premises. Tenant shall use the Premises solely for the Permitted Use specified in the Summary, and shall not use or permit the Premises to be used for any other use or purpose whatsoever without Landlord's prior written approval. Subject to the last sentence of Section 8.2. Tenant shall, at its sole cost and expense, observe and comply with all Laws and all requirements of any board of fire underwriters or similar body relating to the Premises now or hereafter in force relating to or affecting the condition, use, occupancy, alteration or improvement of the Premises (whether, except as otherwise provided herein, structural or nonstructural, including unforeseen and/or extraordinary alterations and/or improvements to the Premises and regardless of the period of time remaining in the Term). Tenant shall not use or allow the Premises to be used for any unlawful purpose. Tenant shall not cause, maintain or permit any nuisance in, on or about the Premises, the Building or the Property, nor commit or suffer to be committed any waste in, on or about the Premises. Without limiting the foregoing, Tenant is prohibited from engaging or permitting others to engage in any activity which would be a violation of any state and/or federal laws relating to the use, sale, possession, cultivation and/or distribution of any controlled substances (whether for commercial or personal purposes) regulated under any applicable law or other applicable law relating to the medicinal use and/or distribution of marijuana (otherwise known as the Compassionate Use Act of 1996) ("**Prohibited Drug Law Activities**").

ARTICLE 10 – HAZARDOUS MATERIALS

As used in this Lease, the term "**Environmental Law(s)**" means any past, present or future federal, state or local Law relating to (a) the environment, human health or safety, including, without limitation, emissions, discharges, releases or threatened releases of Hazardous Materials (as defined below) into the environment (including, without limitation, air, surface water, groundwater or land), or (b) the manufacture, generation, refining, processing, distribution, use, sale, treatment, receipt, storage, disposal, transport, arranging for transport, or handling of Hazardous Materials. As used in this Lease, the term "**Hazardous Materials**" means and includes any hazardous or toxic materials, substances or wastes as now or hereafter designated or regulated under any Environmental Laws including, without limitation, asbestos, petroleum, petroleum hydrocarbons and petroleum based products, urea formaldehyde foam insulation, polychlorinated biphenyls ("**PCBs**"), and freon and other chlorofluorocarbons. Tenant, its agents, officers, directors, shareholders, members, managers, partners, employees, subtenants, assignees, licensees, contractors or invitees (collectively, "**Tenant's Parties**") shall have the right to bring upon, store, handle, generate and otherwise use Hazardous Materials in and about the Premises in connection with its business operations provided that the same comply with (i) the Permitted Use and (ii) all applicable Environmental Laws. Upon the expiration or earlier termination of this Lease, Tenant agrees to promptly remove from the Premises, at its sole cost and expense, any and all Hazardous Materials, including any equipment or systems containing Hazardous Materials which are installed, brought upon, stored, used, generated or released upon, in, under or about the Premises or any portion thereof by Tenant or any of Tenant's Parties. To the fullest extent permitted by law, Tenant agrees to promptly indemnify, protect, defend and hold harmless Landlord and Landlord's members, shareholders, partners, officers, directors, managers, employees, agents, contractors, successors and assigns (collectively, "**Landlord Parties**") from and against any and all claims, damages, judgments, suits, causes of action, losses, liabilities, penalties, fines, expenses and costs (including, without limitation, clean-up, removal, remediation and restoration costs, sums paid in settlement of claims, attorneys' fees, consultant fees and expert fees and court costs) which arise or result from the presence of Hazardous Materials on, in, under or about the Premises or any portion thereof and which are caused or permitted by Tenant or any of Tenant's Parties. Tenant shall give Landlord written notice of any evidence of water leaks or water infiltration in the Premises promptly upon discovery of same. Investigation, clean up and remediation may be performed only after Tenant has Landlord's written approval of a plan for such remediation. All clean up and remediation shall be done in compliance with all applicable Laws and to the reasonable satisfaction of Landlord.

ARTICLE 11- PARKING

During the Term, Tenant shall be entitled, at no charge to Tenant, to utilize all exterior elements of the Premises, including, without limitation, parking spaces and parking and loading areas of the Premises, entrances, drive aisles, sidewalks and landscaping.

ARTICLE 12 - TENANT SIGNS

Subject to Landlord's prior approval (which shall not be unreasonably withheld, conditioned or delayed), any covenants, conditions, and restrictions affecting the Premises and all applicable laws, rules, regulations, and local ordinances, and subject to obtaining all necessary permits and approvals from the City of Fremont, Tenant shall have the right to install and maintain, at Tenant's sole cost and expense, the maximum allowable signage as permitted by the City of Fremont (including exterior identification signage on the Building and on any monument signs now or hereafter located at the Premises), subject to the provisions of this Article 12. Tenant shall be solely responsible for payment of all costs and expenses arising from the Tenant's signage, including, without limitation, all design, fabrication and permitting costs, license fees, installation, maintenance, repair and removal costs. Subsequent changes to Tenant's sign(s) and/or any additional signs, shall be made or installed at Tenant's sole cost and expense, subject to the prior written consent of Landlord (which shall not be unreasonably withheld, conditioned or delayed). Landlord shall have the right to remove any signs or signage material installed in violation of this Article 12, without being liable to Tenant by reason of such removal, and to charge the cost of removal to Tenant as Additional Rent hereunder, payable within ten (10) days after written demand by Landlord. Upon the expiration or earlier termination of this Lease, Tenant shall remove all exterior Tenant identification signage and repair any damage to the Building caused by any such signage at Tenant's sole cost and expense.

ARTICLE 13 - ALTERATIONS

13.1 **Alterations**. In addition to initial Tenant Improvements which shall be governed by the Work Letter Agreement and shall not be considered "Alterations" as defined herein, Tenant may, at its sole cost and expense, make alterations, additions, installations, improvements and decorations to the Premises ("**Alteration(s)**") subject to and upon the following terms and conditions:

a. Intentionally Omitted.

b. Tenant shall not make any Alterations unless Tenant first obtains Landlord's prior written consent, which consent Landlord shall not unreasonably withhold, condition or delay, provided Landlord's prior approval shall not be required for any non-structural alterations that satisfy all of the following conditions (hereinafter a "**Pre-Approved Alteration**"): (i) the costs of such Alterations do not exceed [***]; (ii) to the extent reasonably required by Landlord or by law due to the nature of the work being performed, Tenant delivers to Landlord final plans, specifications, working drawings, permits and approvals for such Alterations at least ten (10) days prior to commencement of the work thereof; (iii) Tenant and such Alterations otherwise satisfy all other conditions set forth in this Section 13.1; and (iv) the making of such Alterations will not otherwise cause a default by Tenant under any provision of this Lease. Tenant shall provide Landlord with ten (10) days' prior written notice before commencing any Alterations. In addition, before proceeding with any Alteration, Tenant's contractors shall obtain, on behalf of Tenant and at Tenant's sole cost and expense: (A) all necessary governmental permits and approvals for the commencement and completion of such Alterations, and (B) if the cost of such Alterations exceeds $[***] and Landlord requests the same, a completion and lien indemnity bond, or other surety satisfactory to Landlord for such Alterations (provided that the parties hereby acknowledge, for the avoidance of doubt, that such bonding requirement shall not apply to any of the phases of the Tenant Improvement Work). Landlord's approval of any plans, contractor(s) and subcontractor(s) of Tenant shall not release Tenant or any such contractor(s) and/or subcontractor(s) from any liability with respect to such Alterations and will create no liability or responsibility on Landlord's part concerning the completeness of such Alterations or their design sufficiency or compliance with Laws.

c. All Alterations shall be performed: (i) in accordance with the plans, specifications and working drawings, if any, approved by Landlord, such approval not to be unreasonably withheld, condition or delayed; (ii) lien-free and in a good and workmanlike manner; (iii) in compliance with all building codes and Laws; (iv) by reputable contractors, subcontractors and vendors selected by Tenant and reasonably approved by Landlord, and (v) in such manner and subject to such rules and regulations as Landlord may from time to time reasonably designate. Tenant shall insure all Alterations under its causes of loss-special form property insurance pursuant to this Lease. If Landlord fails to approve or disapprove any plans submitted to it in accordance with this Article 12, or to approve the same with reasonable conditions, within ten (10) days after submission, then Tenant shall be entitled to send a second notice to Landlord (the "**Second Alterations Notice")** requesting Landlord's approval of such plans and specifications. If Landlord does not respond within five (5) days after receipt of such Second Alterations Notice, such plans shall be deemed approved.

d. Tenant shall pay to Landlord, as Additional Rent, the reasonable costs of Landlord's engineers and other consultants for review of all plans, specifications and working drawings for the Alterations, within thirty (30) days after Tenant's receipt of invoices either from Landlord or such consultants.

e. Throughout the performance of the Alterations, Tenant shall obtain, or cause its contractors to obtain, workers compensation insurance and commercial general liability insurance in compliance with the insurance provisions of this Lease.

13.2 **Removal of Alterations**. All Alterations and the initial Tenant Improvements in the Premises (whether installed or paid for by Landlord or Tenant), shall become the property of Landlord and shall remain upon and be surrendered with the Premises at the end of the Term; provided, however, upon the expiration or earlier termination of this Lease, Tenant shall remove all items described on Schedule 13.1 as "Required Removables", and Landlord may, by written notice delivered to Tenant within thirty (30) days after Landlord's receipt of plans for the initial Tenant Improvements and any Alterations identify those initial Tenant Improvements or Alterations which Landlord shall require Tenant to remove at the end of the Term (any such items on Schedule 13.1 and any Tenant Improvements or Alterations so identified by Landlord being "**Required Removables**"). If Landlord requires Tenant to remove any such Required Removables, Tenant shall, at its sole cost, remove the identified Required Removables on or before the expiration or sooner termination of this Lease and repair any damage to the Premises caused by such removal to its original condition (or, at Tenant's option, Tenant shall pay to Landlord all of Landlord's reasonable costs of such removal and repair). Notwithstanding the foregoing or anything to the contrary contained herein, in no event shall the items listed on Schedule 13.1 as "Items Which May Be Left Behind" ever be deemed to be Required Removables.

13.3 **Liens.** Tenant shall not permit any mechanic's, materialmen's or other liens to be filed against all or any part of the Property, nor against Tenant's leasehold interest in the Premises, by reason of or in connection with any repairs, alterations, improvements or other work contracted for or undertaken by Tenant or any of Tenant's Parties. If any such liens are filed, Tenant shall, at its sole cost, promptly cause such liens to be released of record or bonded so that such lien(s) no longer affect(s) title to the Property. If Tenant fails to cause any such lien to be released or bonded within ten (10) days after filing thereof, Landlord may cause such lien to be released by any means it shall deem proper, including payment in satisfaction of the claim giving rise to such lien, and Tenant shall reimburse Landlord within five (5) business days after receipt of invoice from Landlord, any sum paid by Landlord to remove such liens, together with interest at the Interest Rate from the date of such payment by Landlord.

ARTICLE 14 - TENANT'S INSURANCE

14.1 **Tenant's Insurance**. On or before the earlier of the Early Access Period, the Commencement Date or the date Tenant commences or causes to be commenced any work of any type in the Premises, and continuing during the entire Term, Tenant shall obtain and keep in full force and effect, the following insurance with limits of coverage as set forth in Section 1.14 of the Summary:

a. Special Form (formerly known as "all risk") insurance, including fire and extended coverage, sprinkler leakage (including earthquake sprinkler leakage), vandalism, malicious mischief plus flood coverage upon all personal property, fixtures and equipment of every description and kind owned by Tenant and located in or on the Premises, or for which Tenant is legally liable or installed by or on behalf of Tenant including, without limitation, furniture, equipment and any other personal property, in an amount not less than the full replacement cost thereof.

b. Commercial general liability insurance coverage on an occurrence basis, including personal injury, bodily injury (including wrongful death), broad form property damage, operations hazard, owner's protective coverage, contractual liability (including Tenant's indemnification obligations under this Lease), liquor liability (if Tenant serves alcohol on the Premises), products and completed operations liability. The limits of liability of such commercial general liability insurance may be increased every three (3) years during the Term upon reasonable prior notice by Landlord to an amount reasonably required by Landlord to be commensurate with amount then required by other prudent owners for comparable properties in the area in which the Premises are located.

c. Commercial Automobile Liability covering all owned, hired and non-owned automobiles.

d. Worker's compensation, in statutory amounts and employers' liability, covering all persons employed in connection with any work done in, on or about the Premises for which claims for death, bodily injury or illness could be asserted against Landlord, Tenant or the Premises.

e. Umbrella liability insurance on an occurrence basis, in excess of and following the form of the underlying insurance described in Section 14.1.b. and 14.1.c. and the employer's liability coverage in Section 14.1.d. which is at least as broad as each and every area of the underlying policies. Such umbrella liability insurance shall include pay on behalf of wording, concurrency of effective dates with primary policies, blanket contractual liability, application of primary policy aggregates, and shall provide that if the underlying aggregate is exhausted, the excess coverage will drop down as primary insurance, subject to customary commercially reasonable deductible amounts imposed on umbrella policies.

f. If Tenant's business includes professional services, Tenant shall, at Tenant's expense, maintain in full force and effect professional liability (also known as errors and omissions insurance), covering Tenant and Tenant's employees from work related negligence and liability in trade.

g. Loss of income, extra expense and business interruption insurance in such amounts as will reimburse Tenant for 12 months of direct or indirect loss of earnings attributable to all perils commonly insured against by prudent tenants or attributable to prevention of access to the Premises or any other portion thereof as a result of such perils.

14.2 **Requirements**. Each policy required to be obtained by Tenant hereunder shall: (a) be issued by insurers which are authorized to do business in the state in which the Premises are located and rated not less than Financial Size VIII, and with a Financial Strength rating of A- in the most recent version of Best's Key Rating Guide (provided that, in any event, the same insurance company shall provide the coverages described in Sections 14.1.a. and 14.1.g. above); (b) be in form reasonably satisfactory from time to time to Landlord; (c) name Tenant as named insured thereunder, and shall name Landlord and, at Landlord's request, such other persons or entities of which Tenant has been informed in writing, as additional insureds as to Tenant's other insurance, all as their respective interests may appear; (d) not have a deductible amount exceeding Two Hundred Fifty Thousand Dollars ($250,000.00), which deductible amount shall be deemed self-insured with full waiver of subrogation; (e) specifically provide that the insurance afforded by such policy for the benefit of Landlord and any other additional insureds shall be primary, and any insurance carried by Landlord or any other additional insureds shall be excess and non-contributing; (f) [intentionally omitted]; (g) if commercially obtainable, require the insurer to endeavor to notify Landlord and any other additional insureds in writing not less than thirty (30) days (ten (10) days in the case of cancellation for nonpayment of premium) prior to any material change, reduction in coverage, cancellation or other termination thereof; (h) contain a cross liability or severability of interest endorsement; and (i) be in amounts sufficient at all times to satisfy any coinsurance requirements thereof. Tenant agrees to deliver to Landlord, as soon as practicable after the placing of the required insurance, but in no event later than the date Tenant is required to obtain such insurance as set forth in Section 14.1 above, certificates from the insurance company evidencing the existence of such insurance and Tenant's compliance with the foregoing provisions of this Article 14. Tenant shall cause replacement certificates to be delivered to Landlord not less than five (5) days prior to the expiration of any such policy or policies. If any such initial or replacement certificates are not furnished within the time(s) specified herein, Landlord shall have the right, but not the obligation, to procure such policies and certificates at Tenant's expense.

14.3 **Effect on Insurance**. Tenant shall not do or permit to be done anything which will (a) violate or invalidate any insurance policy or coverage maintained by Landlord or Tenant hereunder, or (b) unreasonably increase the costs of any insurance policy maintained by Landlord. If Tenant's occupancy or conduct of its business in or on the Premises results in any increase in premiums for any insurance carried by Landlord with respect to the Premises, Tenant shall either discontinue the activities affecting the insurance or pay such increase as Additional Rent within thirty (30) days after being billed therefor by Landlord. If any insurance coverage carried by Landlord pursuant to this Lease or otherwise with respect to the Premises shall be cancelled or reduced (or cancellation or reduction thereof shall be threatened) by reason of the use or occupancy of the Premises other than as allowed by the Permitted Use by Tenant or by anyone permitted by Tenant to be upon the Premises, and if Tenant fails to remedy such condition within fifteen (15) business days after notice thereof, Tenant shall be deemed to be in default under this Lease and Landlord shall have all remedies provided in this Lease, at law or in equity, including, without limitation, the right (but not the obligation) to enter upon the Premises and attempt to remedy such condition at Tenant's cost.

ARTICLE 15 - LANDLORD'S INSURANCE

15.1 **Landlord Insurance**. During the Term, Landlord shall maintain property insurance written on a Special Form (formerly known as "all risk") basis covering the Premises (including the Building and all Tenant Improvements and Alterations installed in the Premises including clean rooms and related improvements, but excluding, however, any property insured by Tenant under Section 14.1(a) above, including Tenant's furniture, fixtures, equipment and other personal property), in an amount at least equal to the replacement value of such improvements against damage by fire and standard extended coverage perils and with vandalism and malicious mischief endorsements, rental loss coverage, and, at Landlord's option, earthquake damage coverage, and such additional coverage as Landlord deems appropriate; provided that such other insurance must be commensurate with types and amounts of coverages then required by other prudent owners for comparable properties in the area in which the Premises are located. Landlord shall also carry commercial general liability in such reasonable amounts and with such reasonable deductibles as would be carried by a prudent owner of a similar building in the area in which the Premises are located. At Landlord's option, all such insurance may be carried under any blanket or umbrella policies that Landlord has in force for other buildings and projects. Landlord may, but shall not be obligated to carry any other form or forms of insurance as Landlord or the Mortgagees or ground lessors of Landlord may reasonably determine; provided that such other insurance must be commensurate with types and amounts of coverages then required by other prudent owners for comparable properties in the

area in which the Premises are located. For purposes of Landlord's insurance coverage, Tenant shall provide Landlord, upon request by Landlord (which request may not be made more often than annually), with the estimated value of any and all improvements and Alterations made to the Premises by Tenant for which Landlord is to carry insurance coverage under this Article 15. In addition, Tenant may provide such values to Landlord from time to time for purposes of determining the insurance coverages required to be carried by Landlord under this Article 15. The cost of insurance obtained by Landlord pursuant to this Article 15 including reasonable deductibles as would be carried by a prudent owner of a similar building in the area in which the Premises are located shall be included in Insurance Costs.

15.2 **General Insurance Requirements**. The property insurance policy required to be obtained by Landlord under Section 15.1 above shall: (a) be issued by insurers which are authorized to do business in the state in which the Premises are located and rated not less than Financial Size VIII, and with a Financial Strength rating of A- in the most recent version of Best's Key Rating Guide; (b) be in form reasonably satisfactory from time to time to Tenant; (c) name Landlord as named insured thereunder, and shall name Tenant as lost payee with respect to all Tenant Improvements and Alterations; (d) not have a deductible amount exceeding Two Hundred Fifty Thousand Dollars ($250,000.00), which deductible amount shall be deemed self-insured with full waiver of subrogation; (e) specifically provide that the insurance afforded by such policy for the benefit of Tenant shall be primary, and any insurance carried by Tenant shall be excess and non-contributing; (f) [intentionally omitted]; (g) if commercially obtainable, require the insurer to endeavor to notify Tenant in writing not less than thirty (30) days (ten (10) days in the case of cancellation for nonpayment of premium) prior to any material change, reduction in coverage, cancellation or other termination thereof; (h) contain a cross liability or severability of interest endorsement; and (i) be in amounts sufficient at all times to satisfy any coinsurance requirements thereof. Landlord agrees to deliver to Tenant, upon Tenant's request therefor, certificates from the insurance company evidencing the existence of such property insurance and Landlord's compliance with the foregoing provisions of this Article 15. Landlord shall cause replacement certificates to be delivered to Tenant not less than five (5) days prior to the expiration of any such policy or policies. If any such initial or replacement certificates are not furnished within the time(s) specified herein, Tenant shall have the right, but not the obligation, to procure such policies and certificates at Landlord's expense.

ARTICLE 16 - INDEMNIFICATION AND EXCULPATION

16.1 **Tenant's Assumption of Risk and Waiver**. Except to the extent such matter is not covered by the insurance required to be maintained by Tenant under this Lease and/or except to the extent such matter is attributable to the negligence or willful misconduct of Landlord or Landlord's agents, contractors or employees, Landlord shall not be liable to Tenant, or any of Tenant's Parties for: (i) any damage to property of Tenant, or of others, located in, on or about the Premises, (ii) the loss of or damage to any property of Tenant or of others by theft or otherwise, (iii) any injury or damage to persons or property resulting from fire, explosion, falling ceiling tiles masonry, steam, gas, electricity, water, rain or leaks from any part of the Premises or from the pipes, appliance of plumbing works or from the roof, street or subsurface or from any other places or by dampness or by any other cause of whatsoever nature, (iv) any such damage caused by persons in the Premises, occupants of any other portions of the Premises, or the public, or caused by operations in construction of any private, public or quasi-public work, or (v) any interruption of utilities and services (subject to Section 7.6 above). Landlord shall in no event be liable to Tenant or any other person for any consequential damages, special or punitive damages, or for loss of business, revenue, income or profits and Tenant hereby waives any and all claims for any such damages. Notwithstanding anything to the contrary contained in this Section 16.1, all property of Tenant and Tenant's Parties kept or stored on the Premises, whether leased or owned by any such parties, shall be so kept or stored at the sole risk of Tenant and Tenant shall hold Landlord harmless from any claims arising out of damage to the same, including subrogation claims by Tenant's insurance carriers. Landlord or its agents shall not be liable for interference with light or other intangible rights.

16.2 **Tenant's Indemnification**. Except to the extent caused by the negligence or willful misconduct of Landlord or Landlord's agents, contractors or employees, Tenant shall be liable for, and shall indemnify, defend, protect and hold Landlord and the Landlord Parties harmless from and against, any and all claims, damages, judgments, suits, causes of action, losses, liabilities and expenses, including, without limitation, attorneys' fees and court costs (collectively, "Indemnified Claims"), arising or resulting from (a) any occurrence in the Premises following the date Landlord delivers possession of all or any portion of the Premises to Tenant, (b) the negligence of willful misconduct of Tenant or any of Tenant's Parties; (c) the use of the Premises and conduct of Tenant's business by Tenant or any of Tenant's Parties, or any other activity, work or thing done, permitted or suffered by Tenant or any of Tenant's Parties, in or about the Premises; and/or (d) any default by Tenant as to any obligations on Tenant's part to be performed under the terms of this Lease. The foregoing indemnification shall include, but not be limited to, any injury to, or death of, any person, or any loss of, or damage to, any property on the Premises, whether or not Landlord or any Landlord Parties has or should have knowledge or notice of the defect or conditions causing or contributing to such injury, death, loss or damage. In case any action or proceeding is brought against Landlord or any Landlord Parties by reason of any such Indemnified Claims, Tenant, upon notice from Landlord, shall defend the same at Tenant's expense by counsel approved in writing by Landlord, which approval shall not be unreasonably withheld. Tenant's indemnification obligations under this Section 16.2 and elsewhere in this Lease shall survive the expiration or earlier termination of this Lease. Tenant's covenants, agreements and indemnification in Section 16.1 and this Section 16.2 are not intended to and shall not relieve any insurance carrier of its obligations under policies required to be carried by Tenant pursuant to the provisions of this Lease.

16.3 **Landlord's Waiver**. Except as set forth in Section 21.2 with respect to holdover, Tenant shall in no event be liable to Landlord or any other person for any consequential damages, special or punitive damages, or for loss of business, revenue, income or profits and Landlord hereby waives any and all claims for any such damages

16.4 **Landlord's Indemnification**. Subject to the terms of this Lease, Landlord shall indemnify, defend, protect and hold Tenant and Tenant's Parties harmless from and against, any and all claims, damages, judgments, suits, causes of action, losses, liabilities and expenses, including, without limitation, attorneys' fees and court costs (collectively, "Landlord Indemnified Claims"), arising or resulting from (a) any occurrence in the Premises following expiration or earlier termination of this Lease and Tenant's vacation of the Premises, (b) any negligence or willful misconduct of Landlord or any of the Landlord Parties; and/or (c) any default by Landlord as to any obligations on Landlord's part to be performed under the terms of this Lease or the terms of any contract or agreement to which Landlord is a party or by which it is bound, affecting this Lease or the Premises. In case any action or proceeding is brought against Tenant or any of Tenant's Parties by reason of any such Landlord Indemnified Claims, Landlord, upon notice from Tenant, shall defend the same at Landlord's expense by counsel approved in writing by Tenant, which approval shall not be unreasonably withheld. Landlord's indemnification obligations under this Section 16.3 and elsewhere in this Lease shall survive the expiration or earlier termination of this Lease for a period of twelve (12) months. Landlord's covenants, agreements and indemnification in this Section 16.3 are not intended to and shall not relieve any insurance carrier of its obligations under policies required to be carried by Landlord pursuant to the provisions of this Lease.

ARTICLE 17- CASUALTY DAMAGE/DESTRUCTION

17.1 **Landlord's Rights and Obligations**. If the Building is damaged by fire or other casualty ("**Casualty**") and the Lease is not terminated pursuant to this Article 17, then Landlord shall commence and proceed diligently with the work of repair, reconstruction and restoration of the portion of the Building damaged by such Casualty (excluding the Tenant Improvements and any Alterations, which shall be restored by Tenant as more fully set forth below) to substantially the condition in which the same existed prior to the Casualty ("**Landlord's Restoration Work**") and this Lease shall continue in full force and effect. Within forty five (45) days after the occurrence of such Casualty, Landlord shall deliver to Tenant a written estimate from a reputable contractor engaged by Landlord as to the probable length of time that will be necessary to substantially complete Landlord's Restoration Work (the "**Restoration Estimate**"). If (i) Landlord's contractor estimates in the Restoration Estimate that Landlord's Restoration Work will require longer than twelve (12) months to complete from the date of Casualty, or (ii) Landlord determines that Landlord will not receive insurance proceeds sufficient to complete restoration (provided that Landlord was carrying and maintaining the insurance coverages that it is required to carry under the terms of this Lease), then Landlord may elect to terminate this Lease effective as of the date which is thirty (30) days after Tenant's receipt of Landlord's election to so terminate; provided, however, Tenant may override Landlord's termination election if under (i) above Tenant notifies Landlord that it desires Landlord to reconstruct notwithstanding such restoration period and Tenant agrees that Tenant's Rent will not abate beyond any period of Landlord's rental abatement insurance, or if under (ii) Tenant agrees to pay for any shortfall in Landlord's insurance proceeds to cover the costs of restoration.

17.2 **Tenant's Obligation to Notify**. In the event of any damage or destruction of all or any part of the Premises, Tenant shall promptly notify Landlord thereof.

17.3 **Abatement of Rent**. If as a result of any such damage, repair, reconstruction and/or restoration of the Building, Tenant is prevented from using, and does not use, the Premises or any portion thereof, then Rent shall be abated or reduced, as the case may be, during the period that Tenant continues to be so prevented from using and does not use the Premises or portion thereof, in the proportion that the rentable square feet of the portion of the Premises that Tenant is prevented from using, and does not use, bears to the total rentable square feet of the Premises, from the date of the damage until the date that Landlord's Restoration Work has been completed. Except for abatement of Rent as provided hereinabove, Tenant shall not be entitled to any compensation or damages for loss of, or interference with, Tenant's business or use or access of all or any part of the Premises resulting from any such damage, repair, reconstruction or restoration.

17.4 **Inability to Complete**. Notwithstanding anything to the contrary contained in this Article 17, if Landlord is obligated or elects to repair, reconstruct and/or restore the damaged portion of the Building pursuant to Section 17.1 above, but is delayed from completing such repair, reconstruction and/or restoration beyond the date which is six (6) months after the date estimated by Landlord's contractor in the Restoration Estimate for completion thereof pursuant to Section 17.1 (which date may be extended up to thirty (30) days to the extent Landlord is delayed in completing Landlord's Restoration Work by reason of any causes beyond the reasonable control of Landlord (including, without limitation, delays due to Force Majeure)), then Tenant may elect to terminate this Lease upon thirty (30) days' prior written notice to Landlord unless Landlord completes the restoration within said 30-day notice period, in which case this Lease shall continue in full force and effect.

17.5 **Damage Near End of Term**. Landlord and Tenant shall each have the right to terminate this Lease if any damage to the Building occurs during the last twelve (12) months of the Term and Landlord's contractor estimates in the Restoration Estimate delivered to the parties that the repair, reconstruction or restoration of such damage cannot be completed within the earlier of (a) the scheduled expiration date of the Term, or (b) sixty (60) days after the date of such Casualty.

17.6 **Tenant's Termination Right**. In the event of any damage or destruction which affects Tenant's use and enjoyment of the Premises, if the Restoration Estimate indicates that Landlord's Restoration Work will not be completed within twelve (12) months after the Casualty, Tenant shall have the right to terminate this Lease upon written notice to Landlord given within thirty (30) days after Tenant's receipt of the Restoration Estimate.

17.7 **Waiver of Termination Right**. This Lease sets forth the terms and conditions upon which this Lease may terminate in the event of any damage or destruction. Accordingly, except as expressly provided herein, Tenant hereby waives any and all provisions of applicable Law that provide alternative rights for the parties in the event of damage or destruction (including, without limitation, to the extent the Premises are located in California, the provisions of California Civil Code Section 1932, Subsection 2, and Section 1933, Subsection 4 and any successor statute or laws of a similar nature).

17.8 **Tenant's Restoration Work**. Following Landlord's completion of Landlord's Restoration Work, Tenant shall perform the work necessary to restore Tenant's Alterations (including the Tenant Improvement) to the condition in which the same existed immediately prior to the Casualty (subject to modifications to reflect changes in Tenant's then-current operations and/or requirements) ("**Tenant's Restoration Work**"). Tenant's Restoration Work shall be performed in accordance with the provisions of Article 13 (Alterations). In the event that Tenant does not receive insurance proceeds sufficient to complete Tenant's Restoration Work due to Landlord not having carried and maintained the insurance coverages that it is required to carry under the terms of this Lease, Landlord agrees to pay to Tenant any such shortfall in insurance proceeds to cover the costs of Tenant's Restoration Work. If Landlord fails to pay such costs to Tenant within thirty (30) days after Tenant's request therefor, Tenant shall have the right to offset such amount against the next payment(s) of Monthly Base Rent coming due until Tenant has been credited for the entire amount of such shortfall.

ARTICLE 18 - CONDEMNATION

18.1 **Substantial or Partial Taking**. Subject to the provisions of Section 18.3 below, either party may terminate this Lease if all or any material part of the Premises that would prevent or materially adversely affect Tenant's ability to use the Premises for the Permitted Use is taken or condemned for any public or quasi-public use under law, by eminent domain or private purchase in lieu thereof (a "**Taking**"). The terminating party shall provide written notice of termination to the other party within thirty (30) days after it first receives notice of the Taking. The termination shall be effective as of the effective date of any order granting possession to, or vesting legal title in, the condemning authority. If this Lease is not terminated, Base Rent and all other elements of this Lease which are dependent upon the area of the Premises shall be appropriately adjusted to account for any reduction in the square footage of the Premises. All compensation awarded for a Taking shall be the property of Landlord. The right to receive compensation or proceeds are expressly waived by Tenant, however, Tenant may file a separate claim for Tenant's (i) the unamortized value of improvements installed by Tenant as its expense, (ii) furniture, fixtures, equipment and other personal property, (iii) loss of goodwill and (iv) Tenant's reasonable relocation expenses.

18.2 **Intentionally Omitted**.

18.3 **Temporary Taking**. In the event of a Taking of the Premises or any part thereof for temporary use, (a) this Lease shall be and remain unaffected thereby and Rent shall not abate, and (b) Tenant shall be entitled to receive for itself such portion or portions of any award made for such use with respect to the period of the taking which is within the Term, provided that if such taking shall remain in force at the expiration or earlier termination of this Lease, Tenant shall perform its obligations with respect to surrender of the Premises and shall pay to Landlord the portion of any award which is attributable to any period of time beyond the Term expiration date. For purpose of this Section 18.3, a temporary taking shall be defined as a taking for a period of two hundred seventy (270) days or less.

18.4 **Waiver**. Tenant hereby waives any rights it may have pursuant to any applicable Laws (including, without limitation, to the extent the Premises are located in California, any rights Tenant might otherwise have pursuant to Section 1265.130 of the California Code of Civil Procedure) and agrees that the provisions hereof shall govern the parties' rights in the event of any Taking.

ARTICLE 19 - WAIVER OF CLAIMS; WAIVER OF SUBROGATION

19.1 **Waiver**. Each party hereby waives its rights against the other party for any claims or damages or losses, including any deductibles, which are caused by or result from (a) any occurrence insured under any property insurance policy carried by such waiving party, or (b) any occurrence which would have been covered under any property insurance required to be obtained and maintained by such waiving party under this Lease had such insurance been obtained and maintained as required. The foregoing waiver shall be in addition to, and not a limitation of, any other waivers or releases contained in this Lease.

19.2 **Waiver of Insurers**. Each party shall cause each property insurance policy carried by it to provide that the insurer waives all rights of recovery by way of subrogation against the other party, in connection with any claims, losses and damages covered by such policy. If either party fails to maintain insurance for an insurable loss, such loss shall be deemed to be self-insured with a deemed full waiver of subrogation as set forth in the immediately preceding sentence.

ARTICLE 20 - ASSIGNMENT AND SUBLETTING

20.1 **Restriction on Transfer**. Except with respect to a Permitted Transfer pursuant to Section 20.6 below, Tenant shall not, without the prior written consent of Landlord, which consent Landlord will not unreasonably withhold, conditioned or delayed, assign this Lease or any interest herein or sublet the Premises or any part thereof, or permit the use or occupancy of the Premises by any party other than Tenant (any such assignment, encumbrance, sublease, license or the like being sometimes referred to as a "**Transfer**"). In no event may Tenant encumber or hypothecate this Lease or the Premises. This prohibition against Transfers shall be construed to include a prohibition against any assignment or subletting by operation of law. Any Transfer without Landlord's consent (except for a Permitted Transfer pursuant to Section 20.6 below) shall constitute a default by Tenant under this Lease, and in addition to all of Landlord's other remedies at law, in equity or under this Lease, such Transfer shall be voidable at Landlord's election. Notwithstanding anything to the contrary contained herein, any initial public offering of Tenant's stock and/or any other transfer of the stock of Tenant on a recognized security exchange shall not be considered a Transfer under this Article 20 requiring Landlord's consent.

20.2 **Landlord's Options**. If Tenant desires to effect a Transfer, then at least thirty (30) days prior to the date when Tenant desires the Transfer to be effective (the "**Transfer Date**"), Tenant shall deliver to Landlord written notice ("**Transfer Notice**") setting forth the terms and conditions of the proposed Transfer and the identity of the proposed assignee, sublessee or other transferee (sometimes referred to hereinafter as a "**Transferee**"). Tenant shall also deliver to Landlord with the Transfer Notice, a current financial statement and such evidence of financial responsibility and standing as Landlord may reasonably require of the Transferee, and such other information concerning the business background and financial condition of the proposed Transferee as Landlord may reasonably request. Except with respect to a Permitted Transfer, within fifteen (15) days after Landlord's receipt of any Transfer Notice, and any additional information requested by Landlord pursuant to this Section 20.2, Landlord will notify Tenant of its election to do one of the following: (a) consent to the proposed Transfer subject to such reasonable conditions as Landlord may impose in providing such consent; or (b) refuse such consent, which refusal shall be on reasonable grounds. If Landlord fails to notify Tenant consent or refuse consent to a proposed Transfer prior to the expiration of such fifteen (15) day notice period, and again within five (5) days following receipt of a second written request for consent from Tenant (delivered following the expiration of the initial 15 day notice period), then such proposed Transfer shall be deemed approved by Landlord.

20.3 **Additional Conditions; Excess Rent**. A condition to Landlord's consent to any Transfer will be the delivery to Landlord of a true copy of the fully executed instrument of assignment, sublease, transfer or hypothecation, in form and substance reasonably satisfactory to Landlord, and an original of Landlord's standard consent form (with such modifications thereto as may be reasonably requested by Tenant and/or the proposed Transferee) executed by both Tenant and the proposed Transferee. In addition, Tenant shall pay to Landlord as Additional Rent within thirty (30) days after receipt thereof, without affecting or reducing any other obligations of Tenant hereunder, fifty percent (50%) of any rent or other economic consideration received by Tenant as a result of any Transfer which exceeds, in the aggregate, (i) the total Rent which Tenant is obligated to pay Landlord under this Lease (prorated to reflect obligations allocable to any portion of the Premises subleased) for the applicable period, plus (ii) any reasonable costs incurred by Tenant in connection with such Transfer, including brokerage commissions, attorneys' fees and any additional concessions/expenses including free rent and tenant improvements actually paid by Tenant in connection with such Transfer, which commissions and fees shall, for purposes of the aforesaid calculation, be amortized on a straight-line basis over the term of such assignment or sublease. If Tenant effects a Transfer or requests the consent of Landlord to any Transfer (whether or not such Transfer is consummated), then, upon demand, and as a condition precedent to Landlord's consideration of the proposed assignment or sublease, Tenant agrees to pay Landlord a non-refundable administrative fee of Five Hundred Dollars ($500.00), plus up to an additional One Thousand Five Hundred Dollars ($1,500.00) for Landlord's reasonable attorneys' and paralegal fees and other costs incurred by Landlord in reviewing such proposed assignment or sublease (whether attributable to Landlord's in-house attorneys or paralegals or otherwise). Acceptance of the Five Hundred Dollar ($500.00) administrative fee and/or reimbursement of up to One Thousand Five Hundred Dollars ($1,500.00) for Landlord's attorneys' and/or paralegal fees shall in no event obligate Landlord to consent to any proposed Transfer.

20.4 **Reasonable Disapproval**. Without limiting in any way Landlord's right to withhold its consent on any reasonable grounds, it is agreed that Landlord will not be acting unreasonably in refusing to consent to a Transfer if, in Landlord's reasonable opinion: (a) the proposed assignee does not have the financial capability to fulfill the obligations imposed by the Transfer; or (b) the proposed Transferee is a governmental entity; (c) the proposed Transfer involves a change of use of the Premises or would violate any exclusive use covenant to which Landlord is bound.

20.5 **No Release**. No Transfer, occupancy or collection of rent from any proposed Transferee shall be deemed a waiver on the part of Landlord, or the acceptance of the Transferee as Tenant and no Transfer shall release Tenant of Tenant's obligations under this Lease or alter the primary liability of Tenant to pay Rent and to perform all other obligations to be performed by Tenant hereunder. Landlord may require that any Transferee remit directly to Landlord on a monthly basis, all monies due Tenant by said Transferee, and each sublease shall provide that if Landlord gives said sublessee written notice that Tenant is in default under this Lease, said sublessee will thereafter make all payments due under the sublease directly to or as directed by Landlord, which payments will be credited against any payments due under this Lease. Tenant hereby irrevocably and unconditionally assigns to Landlord all rents and other sums payable under any sublease of the Premises; provided, however, that Landlord hereby grants Tenant a license to collect all such rents and other sums so long as Tenant is not in default under this Lease. Consent by Landlord to one Transfer shall not be deemed consent to any subsequent Transfer. In the event of default by any Transferee of Tenant or any successor of Tenant in the performance of any of the terms hereof beyond any applicable notice and cure periods, Landlord may proceed directly against Tenant without the necessity of exhausting remedies against such Transferee or successor. To the extent the Premises are located in California, Tenant hereby waives (for itself and all persons claiming under Tenant) the provisions of Civil Code Section 1995.310.

20.6 **Permitted Transfers**. Notwithstanding the provisions of Section 20.1 above to the contrary, provided that Tenant is not then in Default, Tenant may assign this Lease or sublet the Premises or any portion thereof (herein, a "**Permitted Transfer**"), without Landlord's consent to any entity that controls, is controlled by or is under common control with Tenant, or to any successor entity resulting from a merger or consolidation with Tenant, or to any person or entity which acquires all or substantially all of the assets of Tenant's (i) business as a going concern of (ii) stock (each, a "**Permitted Transferee**"), provided that: (a) at least thirty (30) days prior to such assignment or sublease (unless such notice is prohibited by applicable law, in which case Tenant shall deliver such notice promptly after such assignment or sublease), Tenant delivers to Landlord a reasonably detailed description of the proposed Transfer and the financial statements and other financial and background information of the assignee or sublessee described in Section 20.2 above; (b) in the case of an assignment, the assignee assumes, in full, the obligations of Tenant under this Lease (or in the case of a sublease, the sublessee of a portion of the Premises or Term assumes, in full, the obligations of Tenant with respect to such portion) pursuant to an assignment and assumption agreement (or a sublease, as applicable) reasonably acceptable to Landlord, a fully executed copy of which is delivered to Landlord within thirty (30) days following the effective date of such assignment or subletting; (c) each guarantor of this Lease (if any) executes a reaffirmation of its guaranty in form satisfactory to Landlord; (d) the tangible net worth of the assignee or sublessee equals or exceeds that of Tenant as of the date immediately preceding the proposed Transfer; (e) Tenant remains fully liable under this Lease; (f) the use of the Premises is pursuant to Section 1.10 of this Lease; (g) such transaction is not entered into as a subterfuge to avoid the restrictions and provisions of this Article 20 and will not violate any exclusive use covenant to which Landlord is bound; and (h) with respect to a subletting only, Tenant and such Permitted Transferee execute Landlord's standard consent to sublease form (with such modifications thereto as may be reasonably requested by Tenant and/or the proposed Transferee); and (i) Tenant is not in Default under this Lease.

ARTICLE 21 - SURRENDER AND HOLDING OVER

21.1 **Surrender of Premises**. Upon the expiration or sooner termination of this Lease, Tenant shall surrender all keys for the Premises and exclusive possession of the Premises to Landlord broom clean and in good condition and repair, reasonable wear and tear excepted (and casualty damage excepted), with all of Tenant's personal property, electronic, fiber, phone and data cabling and related equipment that is installed by or for the exclusive benefit of Tenant (to be removed in accordance with the National Electric Code and other applicable Laws) and those items, if any, of Alterations identified by Landlord pursuant to Section 13.2, removed therefrom and all damage caused by such removal repaired. If Tenant fails to remove by the expiration or sooner termination of this Lease all of its personal property and Alterations identified by Landlord for removal pursuant to Section 13.2, Landlord may, (without liability to Tenant for loss thereof), at Tenant's sole cost and in addition to Landlord's other rights and remedies under this Lease, at law or in equity: (a) remove and store such items in accordance with applicable Law; and/or (b) upon ten (10) days' prior notice to Tenant, sell all or any such items at private or public sale for such price as Landlord may obtain as permitted under applicable Law. Landlord shall apply the proceeds of any such sale to any amounts due to Landlord under this Lease from Tenant (including Landlord's attorneys' fees and other costs incurred in the removal, storage and/or sale of such items), with any remainder to be paid to Tenant.

21.2 **Holding Over**. Tenant will not be permitted to hold over possession of the Premises after the expiration or earlier termination of the Term without the express written consent of Landlord, which consent Landlord may withhold in its sole and absolute discretion. If Tenant holds over after the expiration or earlier termination of the Term with or without the express written consent of Landlord, then, in addition to all other remedies available to Landlord, Tenant shall become a tenant at sufferance only, upon the terms and conditions set forth in this Lease so far as applicable (including Tenant's obligation to pay all Additional Rent under this Lease), but at a Monthly Base Rent equal to [***] percent ([***]%) of the Monthly Base Rent applicable to the Premises immediately prior to the date of such expiration or earlier termination. Any such holdover Rent shall be paid on a per month basis without reduction for partial months during the holdover. Acceptance by Landlord of Rent after such expiration or earlier termination shall not constitute consent to a hold over hereunder or result in an extension of this Lease. This Section 21.2 shall not be construed to create any express or implied right to holdover beyond the expiration of the Term or any extension thereof; provided, however, Tenant shall have the right to holdover for a period of up to [***] days ("**Pre-Approved Holdover Period**") if Tenant provides a minimum of twelve (12) months prior written notice to Landlord and Tenant pays Monthly Base Rent for such holdover period equal to [***] percent ([***]%) of the Monthly Base Rent applicable to the Premises immediately prior to such Pre-Approved Holdover Period. In addition, if Tenant holds over in the Premises for more than [***] days after the expiration of the Term or any Pre-Approved Holdover Period (provided that Landlord has provided Tenant with at least thirty (30) days' prior notice that Landlord has secured an incoming tenant), then Tenant shall be liable, and shall pay to Landlord within ten (10) days after demand, for all losses incurred by Landlord as a result of such holdover, and shall indemnify, defend and hold Landlord and the Landlord Parties harmless from and against all liabilities, damages, losses, claims, suits, costs and expenses (including reasonable attorneys' fees and costs) arising from or relating to any such holdover tenancy, including without limitation, any claim for damages made by a succeeding tenant. Tenant's indemnification obligation hereunder shall survive the expiration or earlier termination of this Lease. The foregoing provisions of this Section 21.2 are in addition to, and do not affect, Landlord's right of re-entry or any other rights of Landlord hereunder or otherwise at law or in equity.

ARTICLE 22 - DEFAULTS

22.1 **Tenant's Default**. The occurrence of any one or more of the following events shall constitute a "**Default**" under this Lease by Tenant:

a. intentionally omitted;

b. the failure by Tenant to make any payment of Rent, Additional Rent or any other payment required to be made by Tenant hereunder, where such failure continues for five (5) business days after written notice thereof from Landlord that such payment was not received when due; provided that if Landlord provides two (2) or more notices of late payment within any twelve (12) month period, then the third failure of Tenant to make any payment of Rent or any other payment required to be made by Tenant hereunder when due in the twelve (12) month period following the second (2nd) such notice shall be an automatic Default without notice from Landlord;

c. the failure by Tenant to observe or perform any of the express covenants or provisions of this Lease to be observed or performed by Tenant, other than as specified in Section 22.1(a) above, where such failure shall continue for a period of thirty (30) days after written notice thereof from Landlord to Tenant; provided, however, that if the nature of Tenant's default is such that it may be cured but more than thirty (30) days are reasonably required for its cure, then Tenant shall not be deemed to be in default if Tenant shall commence such cure within said thirty (30) day period and thereafter diligently prosecute such cure to completion; or

d. A general assignment by Tenant or any guarantor or surety of Tenant's obligations hereunder ("**Guarantor**") for the benefit of creditors;

e. The filing of a voluntary petition in bankruptcy by Tenant or any Guarantor, the filing by Tenant or any Guarantor of a voluntary petition for an arrangement, the filing by or against Tenant or any Guarantor of a petition, voluntary or involuntary, for reorganization, or the filing of an involuntary petition by the creditors of Tenant or any Guarantor, said involuntary petition remaining undischarged for a period of one hundred twenty (120) days;

f. Receivership, attachment, or other judicial seizure of substantially all of Tenant's assets on the Premises, such attachment or other seizure remaining undismissed or undischarged for a period of thirty (30) days after the levy thereof.

Any notice sent by Landlord to Tenant pursuant to this Section 22.1 shall be in lieu of, and not in addition to, any notice required under any applicable Law.

ARTICLE 23 - REMEDIES OF LANDLORD

23.1 **Landlord's Remedies; Termination**. In the event of any such Default by Tenant, in addition to any other remedies available to Landlord under this Lease, at law or in equity (including, without limitation, to the extent the Premises are located in California, the remedies of Civil Code Section 1951.4 and any successor statute or similar Law, which provides that Landlord may continue this Lease in effect following Tenant's breach and abandonment and collect rent as it falls due, if Tenant has the right to sublet or assign, subject to reasonable limitations), Landlord shall have the immediate option to terminate this Lease and all rights of Tenant hereunder and to re-enter the Premises and remove all persons and property from the Premises in accordance with applicable Law; such property may be removed, stored and/or disposed of as permitted by applicable Law and in accordance with Section 21.1 above. If Landlord shall elect to so terminate this Lease, then Landlord may recover from Tenant: (a) the worth at the time of award of any unpaid Rent which had been earned at the time of such termination; plus (b) the worth at the time of the award of the amount by which the unpaid Rent which would have been earned after termination until the time of award exceeds the amount of such rental loss that Tenant proves could have been reasonably avoided; plus (c) the worth at the time of award of the amount by which the unpaid Rent for the balance of the term after the time of award exceeds the amount of such rental loss that Tenant proves could be reasonably avoided; plus (d) any other amount necessary to compensate Landlord for all detriment proximately caused by Tenant's failure to perform its obligations under this Lease, including any costs to return the Premises to the condition required at the end of the Term.

As used in Sections 23.1(a) and 23.1(b) above, the "**worth at the time of award**" is computed by allowing interest at the Interest Rate set forth in the Summary. As used in Section 23.1(c) above, the "worth at the time of award" is computed by discounting such amount at the discount rate of the Federal Reserve Bank of San Francisco at the time of award plus one percent (1%). To the extent the Premises are located in California, Tenant hereby waives for Tenant and all those claiming under Tenant all right now or hereafter existing including, without limitation, any rights under California Code of Civil Procedure Sections 1174 and 1179 and Civil Code Section 1950.7 to redeem by order or judgment of any court or by any legal process or writ, Tenant's right of occupancy of the Premises after any termination of this Lease.

23.2 **Landlord's Remedies; Continuation of Lease; Re-Entry Rights**. In the event of any such Default by Tenant, in addition to any other remedies available to Landlord under this Lease, at law or in equity, Landlord shall also have the right to (a) continue this Lease in effect after Tenant's breach and abandonment and recover Rent as it becomes due (less any net re-letting proceeds), and (b) with or without terminating this Lease, to re-enter the Premises and remove all persons and property from the Premises in accordance with applicable Law; such property may be removed, stored and/or disposed of as permitted by applicable Law and in accordance with Section 21.1 above. No re-entry or taking possession of the Premises by Landlord pursuant to this Section 23.2, and no acceptance of surrender of the Premises or other action on Landlord's part, shall be construed as an election to terminate this Lease unless a written notice of such intention be given to Tenant or unless the termination thereof be decreed by a court of competent jurisdiction. No notice from Landlord or notice given under a forcible entry and detainer statute or similar Laws will constitute an election by Landlord to terminate this Lease unless such notice specifically so states. Notwithstanding any reletting without termination by Landlord because of any Default, Landlord may at any time after such reletting elect to terminate this Lease for any such Default, provided that Tenant shall be entitled to a credit and/or reduction for any net proceeds received by Landlord on account of such re-letting.

23.3 **Landlord's Right to Perform**. Except as specifically provided otherwise in this Lease, all covenants and agreements by Tenant under this Lease shall be performed by Tenant at Tenant's sole cost and expense and without any abatement or offset of Rent. In the event of any Default by Tenant, Landlord may, without waiving or releasing Tenant from any of Tenant's obligations, make such payment or perform such other act as required to cure such Default on behalf of Tenant. All sums so paid by Landlord and all necessary incidental costs incurred by Landlord in performing such other acts shall be payable by Tenant to Landlord within five (5) days after demand therefor as Additional Rent.

23.4 **Rights and Remedies Cumulative**. All rights, options and remedies of Landlord contained in this Article 23 and elsewhere in this Lease shall be construed and held to be cumulative, and no one of them shall be exclusive of the other, and Landlord shall have the right to pursue any one or all of such remedies or any other remedy or relief which may be provided by law or in equity, whether or not stated in this Lease. Nothing in this Article 23 shall be deemed to limit or otherwise affect Tenant's indemnification of Landlord pursuant to any provision of this Lease.

23.5 **Costs Upon Default and Litigation**. Tenant shall pay to Landlord and its Mortgagees as Additional Rent all the expenses incurred by Landlord or its Mortgagees in connection with any default by Tenant hereunder or the exercise of any remedy by reason of any default by Tenant hereunder, including reasonable attorneys' fees and expenses. If Landlord or its Mortgagees shall be made a party to any litigation commenced against Tenant or any litigation pertaining to this Lease or the Premises, at the option of Landlord and/or its Mortgagees, Tenant, at its expense, shall provide Landlord and/or its Mortgagees with counsel approved by Landlord and/or its Mortgagees and shall pay all costs incurred or paid by Landlord and/or its Mortgagees in connection with such litigation.

ARTICLE 24 - ENTRY BY LANDLORD

Landlord and its employees and agents shall at all reasonable times have the right to enter the Premises to inspect the same, to supply any service required to be provided by Landlord to Tenant under this Lease, to exhibit the Premises to prospective lenders or purchasers (or during the last year of the Term, to prospective tenants), to post notices of non-responsibility, and/or to alter, improve or repair the Premises or any portion thereof to the extent Landlord is permitted to make such alterations, improvements or repairs under this Lease, all without being deemed guilty of or liable for any breach of Landlord's covenant of quiet enjoyment or any eviction of Tenant, and without abatement of Rent. In exercising such entry rights, Landlord shall (i) minimize, to the extent reasonably practicable, the interference with Tenant's business, (ii) provide Tenant with least twenty four (24) hours' advance written notice of such entry (except in emergency situations), (iii) comply with Tenant's reasonable safety, security and confidentiality requirements, and (iv) be accompanied by a representative of Tenant (collectively, the "**Access Conditions**"), provided that Tenant hereby covenants and agrees to make a representative available at all times during Tenant's normal business hours during the Term upon twenty four (24) hours' advance written notice. For each of the foregoing purposes, Landlord shall at all times have and retain a key and/or access card with which to unlock all of the doors in, upon and about the Premises, excluding Tenant's vaults, safes and Secure Areas, and Landlord shall have the means which Landlord may deem proper to open said doors in an emergency in order to obtain entry to the Premises. Any entry to the Premises obtained by Landlord by any of said means or otherwise shall not under any circumstances be construed or deemed to be a forcible or unlawful entry into, or a detainer of, the Premises, or an eviction of Tenant from the Premises or any portion thereof, or grounds for any abatement or reduction of Rent and Landlord shall not have any liability to Tenant for any damages or losses on account of any such entry by Landlord. Notwithstanding anything to the contrary set forth in this Article 24, Tenant may designate certain areas of the Premises as "**Secure Areas**" (i) for the purpose of securing certain valuable, proprietary, confidential or otherwise sensitive materials, property and/or information, (ii) in connection with Tenant's manufacturing processes or operations within the Premises or (iii) to comply with applicable Laws. The Secure Areas may include, without limitation, any clean rooms, laboratory areas, warehouse and holding areas or other similar areas located in the Building. Notwithstanding anything to the contrary contained in this Lease, in no event may Landlord enter any Secure Areas except (a) to the extent necessary in order to satisfy its maintenance and/or repair obligations under Section 8.1 above or (b) in response to specific requests by Tenant. In either such event, access by Landlord into any Secure Areas shall nevertheless be subject to the Access Conditions.

ARTICLE 25 - LIMITATION ON LANDLORD'S LIABILITY

Notwithstanding anything contained in this Lease to the contrary, the obligations of either party under this Lease (including as to any actual or alleged breach or default by either party) do not constitute personal obligations of the individual members, managers, investors, partners, directors, officers, or shareholders of such party or such party's members or partners, and the other party shall not seek recourse against the individual members, managers, investors, partners, directors, officers, or shareholders of such party or such party's members or partners or any other persons or entities having any interest in such party, or any of their personal assets for satisfaction of any liability with respect to this Lease. In addition, in consideration of the benefits accruing hereunder to Tenant and notwithstanding anything contained in this Lease to the contrary, Tenant hereby covenants and agrees for itself and all of its successors and assigns that the liability of Landlord for its obligations under this Lease (including any liability as a result of any actual or alleged failure, breach or default hereunder by Landlord), shall be limited solely to, and Tenant's and its successors' and assigns' sole and exclusive remedy shall be against, Landlord's interest in the Premises, and no other assets of Landlord. The term "Landlord" as used in this Lease, so far as covenants or obligations on the part of the Landlord are concerned, shall be limited to mean and include only the owner or owners, at the time in question, of the fee title to, or a lessee's interest in a ground lease of, the Premises. In the event of any transfer or conveyance of any such title or interest (other than a transfer for security purposes only), the transferor shall be automatically relieved of all covenants and obligations on the part of Landlord contained in this Lease. Landlord and Landlord's transferees and assignees shall have the absolute right to transfer all or any portion of their respective title and interest in the Premises and/or this Lease without the consent of Tenant, and such transfer or subsequent transfer shall not be deemed a violation on Landlord's part of any of the terms and conditions of this Lease.

ARTICLE 26 - SUBORDINATION

Tenant accepts this Lease subject and subordinate to any mortgage(s), deed(s) of trust, ground lease(s) or other lien(s) now or subsequently arising upon the Premises, and to renewals, modifications, refinancings and extensions thereof (collectively referred to as a "**Mortgage**"), provided and on the condition that any Mortgagee (as hereinafter defined) shall execute and deliver to Tenant a subordination, non-disturbance and attornment agreement ("**SNDA**") in a commercially reasonable form reasonable acceptable to such Mortgagee and Tenant. This clause shall be self-operative, but no later than ten (10) business days after written request from Landlord or any holder of a Mortgage (each, a "**Mortgagee**" and collectively, "**Mortgagees**"), Tenant shall execute a commercially reasonable subordination agreement. As an alternative, a Mortgagee shall have the right at any time to subordinate its Mortgage to this Lease. No later than ten (10) business days after written request by Landlord or any Mortgagee, Tenant shall, without charge, attorn to and recognize any successor to Landlord's interest in this Lease ("**Successor Landlord**") as Tenant's landlord under this Lease so long as such successor shall recognize the rights of Tenant under this Lease and agrees that Tenant's possession hereunder will not be disturbed. Upon such attornment, this Lease shall continue in full force and effect as a direct lease between the Successor Landlord and Tenant upon all of the terms, conditions and covenants as are set forth in this Lease except that Successor Landlord shall not (a) be liable for any previous act or omission of Landlord under this Lease, unless the same shall be continuing; (b) be subject to any offset, not expressly provided for in this Lease, which theretofore shall have accrued to Tenant against Landlord; or (c) be bound by any previous modification of this Lease or by any previous prepayment of more than one month's Monthly Base Rent or Additional Rent, unless such modification or prepayment shall have been expressly approved in writing by the Mortgagee of the Mortgage through or by reason of which the Successor Landlord shall have succeeded to the rights of Landlord under this Lease. Tenant hereby waives its rights under any current or future Law which gives or purports to give Tenant any right to terminate or otherwise adversely affect this Lease and the obligations of Tenant hereunder in the event of any such foreclosure proceeding or sale. Should Tenant fail to sign and return any such documents within said ten (10) business day period, Tenant shall be in default hereunder. In the event of any conflict between the provisions of this Article 26 and the provisions of any SNDA executed by Tenant and any Mortgagee, the provisions of such SNDA shall govern.

ARTICLE 27 - ESTOPPEL CERTIFICATE

Within ten (10) business days following written request by the other party, Tenant or Landlord shall execute and deliver to the other an estoppel certificate, in a form substantially similar to the form of Exhibit E attached hereto. Any such estoppel certificate delivered pursuant to this Article 27 may be relied upon by Landlord or Tenant, as the case may be, and any mortgagee, beneficiary, purchaser or prospective purchaser of any portion of the Property, as well as their assignees. Either party's failure to deliver such certificate within such time shall be conclusive upon such party that this Lease is in full force and effect, without modification except as may be represented by the party requesting the estoppel, that there are no uncured defaults in performance by either party, and that not more than one (1) month's Rent has been paid in advance.

ARTICLE 28 - RELOCATION OF PREMISES

Intentionally Omitted.

ARTICLE 29 - MORTGAGEE PROTECTION

If, in connection with Landlord's obtaining or entering into any financing or ground lease for any portion of the Premises, the lender or ground lessor shall request modifications to this Lease, Tenant shall, within thirty (30) days after request therefor, execute an amendment to this Lease including such modifications, provided such modifications are reasonable, do not increase the obligations of Tenant hereunder, do not decreases Landlord's obligations hereunder and do not adversely affect the leasehold estate created hereby or Tenant's rights hereunder.

ARTICLE 30 - QUIET ENJOYMENT

Landlord covenants and agrees with Tenant that, provided no Event of Default exists and is continuing, Tenant shall have the right to use and occupy the Premises in accordance with and subject to the terms and conditions of this Lease as against all persons claiming by, through or under Landlord. This covenant shall be binding upon Landlord and its successors only during its or their respective periods of ownership of the Premises.

ARTICLE 31 - MISCELLANEOUS PROVISIONS

31.1 **Broker**. Tenant represents that it has not had any dealings with any real estate broker, finder or intermediary with respect to this Lease, other than the Brokers specified in the Summary. Tenant shall indemnify, protect, defend (by counsel reasonably approved in writing by Landlord) and hold Landlord harmless from and against any and all claims, judgments, suits, causes of action, damages, losses, liabilities and expenses (including attorneys' fees and court costs) resulting from any breach by Tenant of the foregoing representation, including, without limitation, any claims that may be asserted against Landlord by any broker, agent or finder undisclosed by Tenant herein. Landlord shall indemnify, protect, and hold Tenant harmless from and against any and all claims, judgments, suits, causes of action, damages, losses, liabilities and expenses (including attorneys' fees and court costs) resulting from any other brokers claiming to have represented Landlord in connection with this Lease. The foregoing indemnities shall survive the expiration or earlier termination of this Lease. Landlord shall pay to the Brokers the brokerage fee, if any, pursuant to a separate written agreement between Landlord and Brokers.

31.2 **Governing Law**. This Lease shall be governed by, and construed pursuant to, the laws of the state in which the Premises are located. Venue for any litigation between the parties hereto concerning this Lease or the occupancy of the Premises shall be initiated in the county in which the Premises are located. Tenant shall comply with all governmental and quasi-governmental laws, ordinances and regulations applicable to the Premises, and all rules and regulations adopted pursuant thereto and all covenants, conditions and restrictions applicable to and/or of record against the Premises (individually, a "**Law**" and collectively, the "**Laws**").

31.3 **Successors and Assigns**. Subject to the provisions of Article 25 above, and except as otherwise provided in this Lease, all of the covenants, conditions and provisions of this Lease shall be binding upon, and shall inure to the benefit of, the parties hereto and their respective heirs, personal representatives and permitted successors and assigns; provided, however, no rights shall inure to the benefit of any Transferee of Tenant unless the Transfer to such Transferee is made in compliance with the provisions of Article 20, and no options or other rights which are expressly made personal to the original Tenant hereunder or in any rider attached hereto shall be assignable to or exercisable by anyone other than the original Tenant under this Lease.

31.4 **No Merger**. The voluntary or other surrender of this Lease by Tenant or a mutual termination thereof shall not work as a merger and shall, at the option of Landlord, either (a) terminate all or any existing subleases, or (b) operate as an assignment to Landlord of Tenant's interest under any or all such subleases.

31.5 **Professional Fees**. If either Landlord or Tenant should bring suit (or alternate dispute resolution proceedings) against the other with respect to this Lease, including for unlawful detainer, forcible entry and detainer, or any other relief against the other hereunder, then all reasonable, out-of-pocket costs and expenses incurred by the prevailing party therein (including, without limitation, its actual appraisers', accountants', attorneys' and other professional fees, expenses and court costs), shall be paid by the other party, including any and all costs incurred in enforcing, perfecting and executing such judgment and all reasonable costs and attorneys' fees associated with any appeal.

31.6 **Waiver**. The waiver by either party of any breach by the other party of any term, covenant or condition herein contained shall not be deemed to be a waiver of any subsequent breach of the same or any other term, covenant and condition herein contained, nor shall any custom or practice which may become established between the parties in the administration of the terms hereof be deemed a waiver of, or in any way affect, the right of any party to insist upon the performance by the other in strict accordance with said terms. No waiver of any default of either party hereunder shall be implied from any acceptance by Landlord or delivery by Tenant (as the case may be) of any Rent or other payments due hereunder or any omission by the non-defaulting party to take any action on account of such default if such default persists or is repeated, and no express waiver shall affect defaults other than as specified in said waiver.

31.7 **Terms and Headings**. The words "Landlord" and "Tenant" as used herein shall include the plural as well as the singular. Words used in any gender include other genders. The Article and Section headings of this Lease are not a part of this Lease and shall have no effect upon the construction or interpretation of any part hereof. Any deletion of language from this Lease prior to its execution by Landlord and Tenant shall not be construed to raise any presumption, canon of construction or implication, including, without limitation, any implication that the parties intended thereby to state the converse of the deleted language. The parties hereto acknowledge and agree that each has participated in the negotiation and drafting of this Lease; therefore, in the event of an ambiguity in, or dispute regarding the interpretation of, this Lease, the interpretation of this Lease shall not be resolved by any rule of interpretation providing for interpretation against the party who caused the uncertainty to exist or against the draftsman.

31.8 **Time**. Time is of the essence with respect to performance of every provision of this Lease in which time or performance is a factor.

31.9 **Business Day**. A "business day" is Monday through Friday, excluding holidays observed by the United States Postal Service and reference to 5:00 p.m. is to the time zone of the recipient. Whenever action must be taken (including the giving of notice or the delivery of documents) under this Lease during a certain period of time (or by a particular date) that ends (or occurs) on a non-business day, then such period (or date) shall be extended until the immediately following business day.

31.10 **Payments and Notices**. All Rent and other sums payable by Tenant to Landlord hereunder shall be paid to Landlord at the address designated in the Summary, or to such other persons and/or at such other places as Landlord may hereafter designate in writing. Any notice required or permitted to be given hereunder must be in writing and may be given by personal delivery (including delivery by nationally recognized overnight courier or express mailing service), or by registered or certified mail, postage prepaid, return receipt requested, addressed to Tenant at the address(es) designated in the Summary, or to Landlord at the address(es) designated in the Summary. Either party may, by written notice to the other, specify a different address for notice purposes. Notice given in the foregoing manner shall be deemed given (i) when actually received or refused by the party to whom sent if delivered by a carrier or personally served or (ii) if mailed, on the day of actual delivery or refusal as shown by the certified mail return receipt or the expiration of three (3) business days after the day of mailing, whichever first occurs.

31.11 **Prior Agreements; Amendments**. This Lease, including the Summary and all Exhibits attached hereto, contains all of the covenants, provisions, agreements, conditions and understandings between Landlord and Tenant concerning the Premises and any other matter covered or mentioned in this Lease, and no prior agreement or understanding, oral or written, express or implied, pertaining to the Premises or any such other matter shall be effective for any purpose. No provision of this Lease may be amended or added to except by an agreement in writing signed by the parties hereto or their respective successors in interest. The parties acknowledge that all prior agreements, representations and negotiations are deemed superseded by the execution of this Lease to the extent they are not expressly incorporated herein.

31.12 **Separability**. The invalidity or unenforceability of any provision of this Lease shall in no way affect, impair or invalidate any other provision hereof, and such other provisions shall remain valid and in full force and effect to the fullest extent permitted by law.

31.13 **Recording**. Neither Landlord nor Tenant shall record this Lease or a short form memorandum of this Lease.

31.14 **Accord and Satisfaction**. No payment by Tenant or receipt by Landlord of a lesser amount than the Rent payment herein stipulated shall be deemed to be other than on account of the Rent, nor shall any endorsement or statement on any check or any letter accompanying any check or payment as Rent be deemed an accord and satisfaction, and Landlord may accept such check or payment without prejudice to Landlord's right to recover the balance of such Rent or pursue any other remedy provided in this Lease. Tenant agrees that each of the foregoing covenants and agreements shall be applicable to any covenant or agreement either expressly contained in this Lease or imposed by any statute or at common law.

31.15 **Financial Statements**. Upon ten (10) days prior written request from Landlord (which Landlord may make at any time during the Term including in connection with Tenant's exercise of any Option in this Lease, but no more often that two (2) times in any calendar year, other than in the event of a default by Tenant during such calendar year or the exercise of any Option in such calendar year, when such limitation shall not apply), Tenant shall deliver to Landlord for review by Landlord and by Landlord's accountants, investors and prospective purchasers and lenders: (a) a current financial statement of Tenant and any guarantor of this Lease, and (b) financial statements of Tenant and such guarantor for the two (2) years prior to the current financial statement year. Landlord covenants and agrees not to disclose any information regarding Tenant's financial statements to any parties other than its accountants, investors, purchasers, and lenders to keep all of Tenant's financial information confidential. Without limiting the foregoing, Tenant may condition delivery of such financial statements on Landlord's execution and delivery of a Tenant's form of confidentiality agreement. Such statements shall be prepared in accordance with generally acceptable accounting principles and certified as true in all material respects by Tenant (if Tenant is an individual) or by an authorized officer, member/manager or general partner of Tenant (if Tenant is a corporation, limited liability company or partnership, respectively).

31.16 **No Partnership**. Landlord does not, in any way or for any purpose, become a partner of Tenant in the conduct of its business, or otherwise, or joint venturer or a member of a joint enterprise with Tenant by reason of this Lease.

31.17 **Force Majeure**. If either party hereto shall be delayed or hindered in or prevented from the performance of any act required hereunder by reason of strikes, lock-outs, labor troubles, inability to procure materials, failure of power, governmental moratorium or other governmental action or inaction (including, without limitation, failure, refusal or delay in issuing permits, approvals and/or authorizations), injunction or court order, riots, insurrection, war, terrorism, bioterrorism, fire, earthquake, inclement weather including rain, flood or other natural disaster or other reason of a like nature not the fault of the party delaying in performing work or doing acts required under the terms of this Lease (but excluding delays due to financial inability) (herein, "**Force Majeure Delay(s)**"), then performance of such act shall be excused for the period of such Force Majeure Delay and the period for the performance of any such act shall be extended for a period equivalent to the period of such delay. The provisions of this Section 31.17 shall not apply to nor operate to excuse Tenant from the payment of Monthly Base Rent, or any Additional Rent or any other payments strictly in accordance with the terms of this Lease.

31.18 **Counterparts**. This Lease may be executed in one or more counterparts, each of which shall constitute an original and all of which shall be one and the same agreement. Signatures and initials required in this document may be executed via "wet" original handwritten signature or initials, or via electronic signature or mark, which shall be binding on the parties as originals, and the executed signature pages may be delivered using pdf or similar file type transmitted via electronic mail, cloud based server, e-signature technology or other similar electronic means, and any such transmittal shall constitute delivery of the executed document for all purposes of this Lease.

31.19 **Nondisclosure of Lease Terms**. The terms and conditions of this Lease (including any materials, documents or other information furnished by one party to the other party pursuant to this lease) are confidential and may not be disclosed by Landlord or Tenant or to any third parties without the prior written consent of the other party except for such parties' respective attorneys, tax advisors, financial consultants, partners or as may be required by applicable Laws or as may be necessary to enforce the terms of this Lease; provided, however, that Tenant may disclose the terms to prospective subtenants or assignees under this Lease.

31.20 **Tenant's Authority**. If Tenant executes this Lease as a partnership, corporation or limited liability company, then Tenant and the persons and/or entities executing this Lease on behalf of Tenant represent and warrant that: (a) Tenant is a duly organized and existing partnership, corporation or limited liability company, as the case may be, and is qualified to do business in the state in which the Premises are located; (b) such persons and/or entities executing this Lease are duly authorized to execute and deliver this Lease on Tenant's behalf; and (c) this Lease is binding upon Tenant in accordance with its terms. Tenant shall provide to Landlord a copy of any documents reasonably requested by Landlord evidencing such qualification, organization, existence and authorization within ten (10) days after Landlord's request. Tenant represents and warrants to Landlord that Tenant is not, and the entities or individuals constituting Tenant or which may own or control Tenant or which may be owned or controlled by Tenant are not, (i) in violation of any Laws relating to terrorism or money laundering, or (ii) among the individuals or entities identified on any list compiled pursuant to Executive Order 13224 for the purpose of identifying suspected terrorists or on the most current list published by the U.S. Treasury Department Office of Foreign Assets Control at its official website, http://www.treas.gov/ofac/tllsdn.pdf or any replacement website or other replacement official publication of such list.

31.21 **Joint and Several Liability**. If more than one person or entity executes this Lease as Tenant: (a) each of them is and shall be jointly and severally liable for the covenants, conditions, provisions and agreements of this Lease to be kept, observed and performed by Tenant; and (b) the act or signature of, or notice from or to, any one or more of them with respect to this Lease shall be binding upon each and all of the persons and entities executing this Lease as Tenant with the same force and effect as if each and all of them had so acted or signed, or given or received such notice.

31.22 **No Option**. The submission of this Lease for examination or execution by Tenant does not constitute a reservation of or option for the Premises and this Lease shall not become effective as a Lease until it has been executed by Landlord and delivered to Tenant.

31.23 **OFAC**. Tenant certifies, represents, warrants and covenants that:

It is not acting and will not act, directly or indirectly, for or on behalf of any of the following:

a. Any person, group, entity, or nation named by any Executive Order or the United States Treasury Department as a terrorist;

b. Any “Specially Designated National” or “Blocked Person” as designated pursuant to any law, order, rule, or regulation that is enforced or administered by the United States Government or any of its departments or agencies; or

c. Any other banned or blocked person, entity, nation or transaction pursuant to any law, order, rule, or regulation that is enforced or administered by the Office of Foreign Assets Control; and

It is not engaged in this transaction, directly or indirectly on behalf of, or instigating or facilitating this transaction, directly or indirectly on behalf of, any such person, group, entity or nation.

[NO FURTHER TEXT ON THIS PAGE; SIGNATURES ON FOLLOWING PAGE]

IN WITNESS WHEREOF, Landlord and Tenant have caused this Lease to be executed the date first above written.

Tenant:

ORCHARD THERAPEUTICS NORTH AMERICA,
a California corporation

By: /s/ Mark Rothera
Name: Mark Rothera
Title: President & CEO

[SIGNATURE CONTINUED ON FOLLOWING PAGE]

Landlord:

BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC,
a Delaware limited liability company

By:_____
Its: Authorized Signatory

For LBA Office Use Only: Prepared & Reviewed by: _____

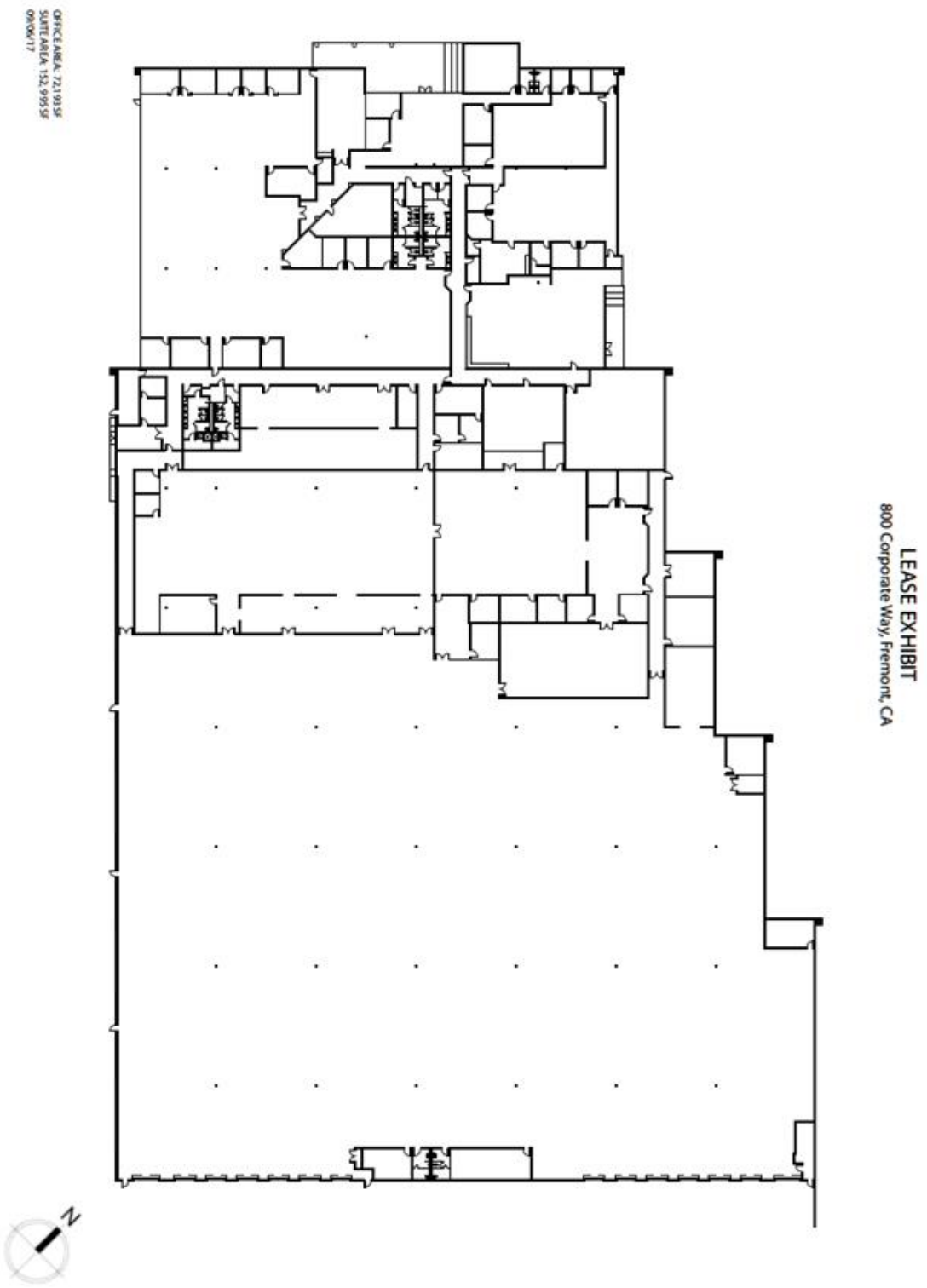
EXHIBIT A

PREMISES SITE PLAN

*** Confidential Treatment Requested ***

EXHIBIT B

PREMISES FLOOR PLAN



*** Confidential Treatment Requested ***

EXHIBIT C

WORK LETTER
[TENANT BUILD W/ALLOWANCE]

1. **TENANT IMPROVEMENTS**. As used in the Lease and this Work Letter, the term "**Tenant Improvements**" or "**Tenant Improvement Work**" or "**Tenant's Work**" means the completion of the Roof Work and the HVAC Work as well as completion of those items of general tenant improvement construction shown on the Final Plans (described in Section 4 below), more particularly described in Section 5 below. Tenant shall complete the Tenant Improvements at Tenant's sole cost and expense, subject to application of Landlord's Allowance described below.

2. **WORK SCHEDULE**. Prior to commencing construction, Tenant will deliver to Landlord a schedule ("**Work Schedule**"), which will set forth the then-anticipated timetable for the planning and completion of the installation of the Tenant Improvements. It is understood that (i) Tenant intends to complete the construction and design of the Tenant Improvements in multiple phases (ii) the Work Schedule shall be subject to modification by Tenant from time to time. Tenant agrees that once it commences any phase of Tenant Improvements Tenant shall pursue completion of such phase of the Tenant Improvements with due diligence.

3. **CONSTRUCTION REPRESENTATIVES**. Landlord hereby appoints the following person(s) as Landlord's representative ("**Landlord's Representative**") to act for Landlord in all matters covered by this Work Letter: [***].

Tenant hereby appoints the following person(s) as Tenant's representative ("**Tenant's Representative**") to act for Tenant in all matters covered by this Work Letter: [***].

All communications with respect to the matters covered by this Work Letter are to be made to Landlord's Representative or Tenant's Representative, as the case may be, in writing in compliance with the notice provisions of the Lease. Either party may change its representative under this Work Letter at any time by written notice to the other party in compliance with the notice provisions of the Lease.

4. **TENANT IMPROVEMENT PLANS**

(a) **Preparation of Space Plans**. In accordance with the Work Schedule, Landlord agrees to meet with Tenant's architect and/or space planner for the purpose of promptly reviewing preliminary space plans for the layout of the Premises prepared by Tenant ("**Space Plans**"). The Space Plans are to be sufficient to convey the architectural design of the Premises and layout of the Tenant Improvements therein and are to be submitted to Landlord in accordance with the Work Schedule for Landlord's approval. Landlord shall approve or reasonably disapprove the Space Plans within [***] days following receipt from Tenant, failing which Tenant may send a second request for such approval. If Landlord fails to approve or reasonably disapprove such Space Plans within such [***] day period, then if Landlord fails to approve or reasonably disapprove such Space Plans within [***] business days after receipt of a second request for approval, then such Space Plans shall be deemed approved. If Landlord reasonably disapproves any aspect of the Space Plans, Landlord will advise Tenant in writing of such disapproval and the reasons therefor. Tenant will then submit to Landlord for Landlord's approval a redesign of the Space Plans incorporating the revisions reasonably required by Landlord.

(b) **Preparation of Final Plans**. Based on the approved Space Plans, and in accordance with the Work Schedule, Tenant's architect will prepare complete architectural plans, drawings and specifications and complete engineered mechanical, structural and electrical working drawings for all of the Tenant Improvements for the Premises (collectively, the "**Final Plans**"). The Final Plans will show (a) the subdivision (including partitions and walls), layout, lighting, finish and decoration work (including carpeting and other floor coverings) for the Premises; (b) all internal and external communications and utility facilities which will require conduiting or other improvements from the base Building shell work and/or within common areas; and (c) all other specifications for the Tenant Improvements. The Final Plans will be submitted to Landlord for signature to confirm that they are consistent with the Space Plans. Landlord shall approve or reasonably disapprove the Final Plans within [***] days following receipt from Tenant, failing which Tenant may send a second request for such approval. If Landlord fails to approve or reasonably disapprove such Final Plans within [***] business days after receipt of such second request, then such Final Plans shall be deemed approved. If Landlord reasonably disapproves any aspect of the Final Plans based on any inconsistency with the Space Plans, Landlord agrees to advise Tenant in writing of such disapproval and the reasons therefor. Tenant will then cause Tenant's architect to redesign the Final Plans incorporating the revisions reasonably requested by Landlord so as to make the Final Plans consistent with the Space Plans.

(c) **Requirements of Tenant's Final Plans**. Tenant's Final Plans will include locations and complete dimensions, and the Tenant Improvements, as shown on the Final Plans, will: (i) be compatible with the Building shell and with the design, construction and equipment of the Building; and (ii) comply with all applicable laws, ordinances, rules and regulations of all governmental authorities having jurisdiction, and all applicable insurance regulations.

(d) **Submittal of Final Plans**. Once approved by Landlord and Tenant, Tenant's architect will submit the Final Plans to the appropriate governmental agencies for plan checking and the issuance of a building permit. Tenant's architect, with Landlord's cooperation, will make any changes to the Final Plans which are requested by the applicable governmental authorities to obtain the building permit. Subject to Section 5(c) below, after approval of the Final Plans no further changes may be made to the same by Tenant without the prior written approval of Landlord, which approval shall not be unreasonably withheld, conditioned or delayed.

(e) **Changes to Shell of Building**. If the Final Plans or any amendment thereof or supplement thereto shall require changes in the Building shell, the increased cost of the Building shell work caused by such changes will be paid for by Tenant or charged against the "Allowance" described in Section 5 below.

(f) **Work Cost Estimate and Statement**. Prior to the commencement of construction of any of the Tenant Improvements shown on the Final Plans, Tenant will submit to Landlord a written estimate of the cost to complete the Tenant Improvement Work, which written estimate will be based on the Final Plans taking into account any modifications which may be required to reflect changes in the Final Plans required by the City or County in which the Premises are located (the "**Work Cost Estimate**"). Submission of the Work Cost Estimate will proceed in accordance with the Work Schedule. Tenant agrees to pay for all costs for design, permits, materials, construction and installation of the Tenant Improvements, provided Landlord will provide the Allowance referenced in the Summary per Section 5 below which Tenant may apply to the cost of the Tenant Improvements.

(g) **Phased Design**. The parties acknowledge and agree that the design of the Tenant Improvements will likely be completed in multiples phases. Therefore, the procedures set forth in this Section 4 shall apply separately with respect to each such phase of the design of the Tenant Improvements.

5. **PAYMENT FOR THE TENANT IMPROVEMENTS**

(a) **Allowance**. Landlord hereby grants to Tenant an Allowance as referenced in the Summary. The Allowance is to be used only for:

(i) Payment of the cost of preparing the Space Plans and the Final Plans, including mechanical, electrical, plumbing and structural drawings and of all other aspects necessary to complete the Final Plans. The Allowance will not be used for payments to any other consultants, designers or architects other than Landlord's architect and/or Tenant's architect.

(ii) The payment of plan check, permit and license fees relating to construction of the Tenant Improvements.

(iii) Construction of the Tenant Improvements, including, without limitation, the following:

(aa) Installation within the Premises of all partitioning, doors, floor coverings, ceilings, wall coverings and painting, millwork and similar items;

(bb) All electrical wiring, lighting fixtures, outlets and switches, and other electrical work necessary for the Premises;

(cc) The furnishing and installation of all duct work, terminal boxes, diffusers and accessories necessary for the heating, ventilation and air conditioning systems within the Premises, including the cost of meter and key control for after-hour air conditioning;

(dd) Any additional improvements to the Premises required for Tenant's use of the Premises including, but not limited to, odor control, special heating, ventilation and air conditioning, noise or vibration control or other special systems or improvements, clean room facilities and equipment;

(ee) All fire and life safety control systems such as fire walls, sprinklers, halon, fire alarms, including piping, wiring and accessories, necessary for the Premises;

(ff) All plumbing, fixtures, pipes and accessories necessary for the Premises;

(gg) Testing and inspection costs;

(hh) Fees and costs payable to Tenant's contractor attributable to general conditions associated with the construction of the Tenant Improvements, plus a construction administration fee equal to [***] ("**Construction Administration Fee**") payable to Landlord to cover the services of Landlord's tenant improvement coordinator; and

(ii) Demolition of any existing improvements in the Premises.

(b) **Excess Costs**. Tenant shall be solely responsible for payment of all fees and costs for the Tenant Improvements, including Landlord's Construction Administration Fee, subject only to application of the Allowance as provided in subparagraph (f) below. Landlord's Construction Administration Fee shall be paid by Tenant to Landlord monthly within five (5) business days after invoice therefor throughout the course of construction based on the hard cost of the Tenant Improvement Work incurred by Tenant for the immediately preceding month. In no event will the Allowance be used to pay for Tenant's furniture, artifacts, equipment, telephone systems or any other item of personal property which is not affixed to the Premises.

(c) **Changes**. Any changes to the Final Plans which are structural in nature or related to the life/safety elements of the Tenant Improvements ("**Updated Plans**") will be prepared by Tenant's architect and subject to Landlord's approval, which shall not be unreasonably withheld, conditioned or delayed. Landlord shall approve or reasonably disapprove (as described in the following sentence) any Updated Plans within [***] business days after submission thereof by Tenant to Landlord, failing which such Updated Plans shall be deemed approved. If Landlord reasonably disapproves any Updated Plans, Landlord will advise Tenant in writing of such disapproval and the reasons therefor within such [***] period, and Tenant may thereafter further update the Final Plans and re-submit the same to Landlord in accordance with this Section 5(c). Tenant shall be solely responsible for any additional costs associated with such changes including the Construction Administration Fee, which fee shall be paid to Landlord within [***] business days after invoice therefor. In the event any such Updated Plans are approved or deemed approved, then "Final Plans" shall be deemed to mean the original Final Plans as modified by such Updated Plans.

(d) **Governmental Cost Increases**. If increases in the cost of the Tenant Improvements as set forth in the Work Cost Statement are due to requirements of any governmental agency, Tenant shall be solely responsible for such additional costs including the Construction Administration Fee, which fee shall be paid to Landlord within [***] business days after invoice therefor; provided, however, that Landlord will first apply toward any such increase any remaining balance of the Allowance.

(e) **Unused Allowance Amounts**. Any unused portion of the Allowance upon completion of the Tenant Improvements will not be refunded to Tenant or be available to Tenant as a credit against any obligations of Tenant under the Lease.

(f) **Disbursement of the Allowance**. Provided Tenant is not in default following the giving of notice and passage of any applicable cure period under the Lease or this Work Letter, Landlord shall disburse the Allowance to Tenant once Tenant has expended $[***] for actual construction costs which Tenant incurs in connection with the construction of the Tenant Improvements. Landlord shall disburse the Allowance to Tenant when Tenant provides Landlord the following "**Evidence of Completion and Payment**":

(A) [***];

(B) The architect for the Tenant Improvements has certified to Landlord that the Tenant Improvements have been completed [***] in accordance with the Final Plans; and

(C) Tenant has delivered to Landlord such other evidence of Tenant's payment of the general contractor and subcontractors [***] and the absence of any liens generated by such portions of the Tenant's Work as may be required by Landlord (i.e., unconditional lien releases in accordance with California Civil Code Sections 8120 through 8138 or release bond(s) in accordance with California Civil Code Sections 8424 and 8534).

[***].

(g) **Books and Records**. At its option, Landlord, at any time within [***] after [***], and upon at least [***] days prior written notice to Tenant, may cause an audit to be made of Tenant's books and records relating to Tenant's expenditures in connection with the construction of the Tenant Improvements. Tenant shall maintain complete and accurate books and records in accordance with generally accepted accounting principles of these expenditures for at least [***]. Tenant shall make available to Landlord's auditor at the Premises within [***] business days following Landlord's notice requiring the audit, all books and records maintained by Tenant pertaining to the construction and completion of the Tenant Improvements. In addition to all other remedies which Landlord may have pursuant to the Lease, Landlord may recover from Tenant the reasonable cost of its audit if the audit discloses that Tenant falsely reported to Landlord expenditures which were not in fact made or falsely reported a material amount of any expenditure or the aggregate expenditures.

(h) **Security for Tenant's Completion of and Payment for Tenant Improvements**. At least fifteen (15) days prior to commencing construction of any Tenant Improvements, [***] shall deliver the sum of [***] ("**Tenant Construction Funds**") into a construction escrow account (the "**Construction Escrow**") with Commonwealth Title Insurance and Escrow Company ("**Escrow Holder**"), to be held as security until [***] as shown on Tenant's initial Final Plans (but specifically excluding, without limitation, [***]. Concurrently herewith, Landlord, Tenant and Escrow Holder have executed the construction fund escrow agreement attached hereto as Schedule C-3 (the "**Escrow Agreement**") [***]. For the avoidance of doubt, the parties acknowledge and agree that (i) [***] and (ii) [***]. Notwithstanding the foregoing or anything to the contrary contained in this Section 5(h), the escrow obligations set forth in this Section 5(h) shall cease and be of no further force effect at such time as all of the Tenant Construction Funds and all interest earned thereon shall have been disbursed to Tenant.

6. **CONSTRUCTION OF TENANT IMPROVEMENTS**. Following Landlord's approval of the Final Plans, Tenant's contractor (selected as provided in Section 8(n)) will commence and diligently proceed with the construction of the Tenant Improvements; provided, however, that Landlord hereby acknowledges and agrees that the Tenant Improvements may be performed in phases, and nothing herein shall require Tenant to complete the entirety of the Tenant Improvements before a certain date. Tenant shall use diligent efforts to cause its contractor to complete the Tenant Improvements in a good and workmanlike manner in accordance with the Final Plans and the Work Schedule. Tenant agrees to use diligent efforts to cause construction of the Tenant Improvements to commence promptly following the issuance of a building permit for the Tenant Improvements. Landlord shall have the right to enter upon the Premises to inspect Tenant's construction activities following reasonable advance notice Tenant.

7. **MISCELLANEOUS CONSTRUCTION COVENANTS**

(a) **No Liens**. Tenant shall not allow the Tenant Improvements or the Building or any portion thereof to be subjected to any mechanic's, materialmen's or other liens or encumbrances arising out of the construction of the Tenant Improvements.

(b) **Diligent Construction**. Tenant will promptly and diligently pursue construction of each phase of the Tenant Improvements to successful completion in full compliance with the Final Plans, the Work Schedule and this Work Letter. Landlord and Tenant shall cooperate with one another during the performance of Tenant's Work to effectuate such work in a timely and compatible manner.

(c) **Compliance with Laws**. Tenant will construct the Tenant Improvements in a safe and lawful manner. Tenant shall, at its sole cost and expense, comply with all applicable laws and all regulations and requirements of, and all licenses and permits issued by, all municipal or other governmental bodies with jurisdiction which pertain to the installation of the Tenant Improvements. Copies of all filed documents and all permits and licenses shall be provided to Landlord. Any portion of the Tenant Improvements which is not acceptable to any applicable governmental body, agency or department shall be promptly repaired or replaced by Tenant at Tenant's expense. Notwithstanding any failure by Landlord to object to any such Tenant Improvements, Landlord shall have no responsibility therefor.

(d) **Indemnification**. Subject to the terms of the Lease regarding insurance and waiver of subrogation by the parties, Tenant hereby indemnifies and agrees to defend and hold Landlord, the Premises and the Building harmless from and against any and all suits, claims, actions, losses, costs or expenses of any nature whatsoever, together with reasonable attorneys' fees for counsel of Landlord's choice, arising out of or in connection with the Tenant Improvements or the performance of Tenant's Work (including, but not limited to, claims for breach of warranty, worker's compensation, personal injury or property damage, and any materialmen's and mechanic's liens).

(e) **Insurance**. Construction of the Tenant Improvements shall not proceed without Tenant first providing to Landlord evidence of insurance as described on Schedule C-1 attached hereto. Not less than thirty (30) days before commencing the construction of the Tenant Improvements, certificates of such insurance shall be furnished to Landlord or, if requested, the original policies thereof shall be submitted for Landlord's approval. All such policies shall provide that thirty (30) days prior notice must be given to Landlord before modification, termination or cancellation. All insurance policies maintained by Tenant pursuant to this Work Letter shall name Landlord and any lender with an interest in the Premises as additional insureds and comply with all of the applicable terms and provisions of the Lease relating to insurance. Tenant's contractor shall be required to maintain the same insurance policies as Tenant, and such policies shall name Tenant, Landlord and any lender with an interest in the Premises as additional insureds.

(f) **Construction Defects**. Landlord shall have no responsibility for the Tenant Improvements and Tenant will remedy, at Tenant's own expense, and be responsible for any and all defects in the Tenant Improvements that may appear during or after the completion thereof whether the same shall affect the Tenant Improvements in particular or any parts of the Premises in general. Tenant shall indemnify, hold harmless and reimburse Landlord for any costs or expenses incurred by Landlord by reason of any defect in any portion of the Tenant Improvements constructed by Tenant or Tenant's contractor or subcontractors, or by reason of inadequate cleanup following completion of the Tenant Improvements.

(g) **Intentionally Omitted**.

(h) **Labor**. Nothing in this Work Letter shall require Tenant to use union labor.

(i) **Intentionally Omitted**.

(j) **HVAC Systems**. Tenant agrees to be entirely responsible for the maintenance or the balancing of any heating, ventilating or air conditioning system installed by Tenant and/or maintenance of the electrical or plumbing work installed by Tenant and/or for maintenance of lighting fixtures, partitions, doors, hardware or any other installations made by Tenant.

(k) **Coordination with Lease**. Nothing herein contained shall be construed as (i) constituting Tenant as Landlord's agent for any purpose whatsoever, or (ii) a waiver by Landlord or Tenant of any of the terms or provisions of the Lease. Any default by Tenant following the giving of notice and the passage of any applicable cure period with respect to any portion of this Work Letter shall be deemed a breach of the Lease for which Landlord shall have all the rights and remedies as in the case of a breach of said Lease.

(l) **Approval of Plans**. Landlord will not check Tenant drawings for building code compliance. Approval of the Final Plans by Landlord is not a representation that the drawings are in compliance with the requirements of governing authorities, and it shall be Tenant's responsibility to meet and comply with all federal, state, and local code requirements. Approval of the Final Plans does not constitute assumption of responsibility by Landlord or its architect for their accuracy, sufficiency or efficiency, and Tenant shall be solely responsible for such matters.

(m) **Tenant's Deliveries**. Tenant shall deliver to Landlord, at least [***] days prior to the commencement of construction of Tenant's Work, the following information:

(i) The names, addresses, telephone numbers, and primary contacts for the general, mechanical and electrical contractors Tenant intends to engage in the performance of Tenant's Work; and

(ii) The date on which Tenant's Work will commence, together with the estimated dates of completion of Tenant's construction and fixturing work to the extent any such estimated completion dates have been determined.

(n) **Qualification of Contractors**. Once the Final Plans have been proposed and approved, Tenant shall select and retain a contractor, subcontractors and vendors (such as HVAC engineers), subject to approval by Landlord, not to be unreasonably withheld, conditioned or delayed (Landlord hereby approving Tenant's use of the following general contractors: Dome Construction; XL Construction; Truebeck Construction; Rusciano Construction; TICO Construction; and Technical Builders, subject to Landlord's approval of the named contractors' pre-qualification packages and insurance as outlined in Schedule C-1 attached hereto to be provided to Landlord), in connection with all aspects of the design and construction of the Tenant Improvement Work in accordance with the Final Plans. All contractors, subcontractors and vendors engaged by Tenant shall be bondable and licensed, possessing good labor relations, capable of performing quality workmanship and working in harmony with Landlord's general contractor and other contractors on the job, if any, all as reasonably determined by Landlord. All Tenant Improvement Work shall be coordinated with any ongoing general construction work on the Site or in the Building, if any.

(o) **Warranties**. Tenant shall cause its contractor to provide warranties for not less than one (1) year (or such shorter time as may be customary and available without additional expense to Tenant) against defects in workmanship, materials and equipment, which warranties shall run to the benefit of Landlord or shall be assignable to Landlord to the extent that Landlord is obligated to maintain any of the improvements covered by such warranties.

(p) **As-Built Drawings**. Tenant shall cause "As-Built Drawings" (excluding furniture, fixtures and equipment) to be delivered to Landlord and/or Landlord's representative no later than [***] days after the completion of Tenant's Work. In the event these drawings are not received by such date, Landlord may, at its election, cause said drawings to be obtained and Tenant shall pay to Landlord, as additional rent, the cost of producing these drawings.

SCHEDULE C-1

CONTRACTOR INSURANCE REQUIREMENTS

By signing above, the parties acknowledge and agree that they have and will provide proof of the required insurance Coverage as described showing the proper ownership entity as described above on the required certificates.

A. **CONTRACTOR'S AND SUBCONTRACTOR'S INSURANCE COVERAGE REQUIRED**

Insurance shall be placed with insurance companies rated at least A-: XII by Best's Key Rating Guide. Contractor shall cause all of its subcontractors to comply with the coverage and limit requirements of this Exhibit "D", unless different limits are specifically negotiated with Owner. If Owner or LBA determines in its reasonable judgment that additional insurance or additional excess liability insurance is required for certain projects, Contractor shall procure such additional insurance and provide evidence of same to LBA prior to commencing work on such projects.

(i) **Workers' Compensation**

(a) Statutory in accordance with the laws of the state with jurisdiction, including Voluntary Compensation, Broad Form All States Endorsement, U.S. Longshoremen's and Harbor Workers' Coverage and Maritime Coverage, as applicable.

(b) Employer's Liability with limits of not less than (1) $1,000,000 each accident/injury, $500,000 each employee/disease and $500,000 disease/policy limit, or (2) current limit carried, whichever is greater.

(c) Such policy shall include a waiver of subrogation in favor of Owner and LBA.

(ii) **Commercial General Liability – ISO Form CG001 (10/01)**
Occurrence Form Only -("Claims Made" is not acceptable).

(a) Bodily Injury Liability and Property Damage Liability: As required by Section C, below.

(b) General Liability insurance must include Blanket Contractual Liability, Broad Form Liability including Products/Completed Operations, Independent Contractors, Broad Form Property Damage, Personal Injury, Fellow Employee Exclusion deleted, "X", "C" and "U" Exclusions deleted, Incidental Medical Malpractice and Host Liquor. If policy is subject to a "general aggregate," it must contain a per job or per location aggregate extension with respect to the Work for Owner. Contractor's coverage for Completed Operations on the Work must be maintained for five (5) years following completion of the Work and certificates evidencing this coverage must be provided to Owner until the end of such five (5) year period.

(iii) **Automobile Liability**

Bodily Injury Liability and Property Damage Liability in an amount not less than $1,000,000 Each Person, and $2,000,000 Each Accident. The insurance must include Owned (Long Term Leased), Employer's Non-Owned and Hired Automobile Coverage.

(iv) **Excess/Umbrella Liability**

The Umbrella policy shall be in excess of items (i)(b), (ii)(a), ii(b) and (iii) above, with coverages not more restrictive than the primary insurance.

(v) **Property Insurance**

Contractor shall maintain "Special Form" (commonly referred to as "all risk" or "special perils" coverage) property insurance in an amount equal to the full replacement cost of all Contractor's real and personal property (for which it has title and/or risk of loss), as well as real and personal property which becomes a final part of the Project, during its off-Project status, in transit and while stored or worked upon away from, or on, the Project site. Owner and all Indemnitees shall be loss payees under such insurance and such insurance shall contain a waiver of subrogation in favor of Owner and all Indemnitees. All policy proceeds shall be used for the repair or replacement of the property damaged or destroyed.

(vi) **Other Insurance and Requirements**

(a) Contractor Subcontractors shall carry their own "Contractor's Equipment" coverage insuring the full replacement cost of their tools and equipment on an "All Risk" basis and shall contain a Waiver of Subrogation endorsement in favor of Owner and LBA.

(b) If Design/Build Subcontractors are used in the performance of any portion of the Work, then all such Design/Build Subcontractors shall maintain Errors and Omissions Liability Insurance including contractual and prior acts coverage sufficient to cover all Design/Build Work performed by such Design/Build Subcontractors under the Agreement with limits of liability of not less than $1,000,000 per claim and in the aggregate, or limit carried, whichever is greater, and shall include a contractual liability endorsement and a deductible amount not greater than $50,000. Such insurance shall be maintained during the term of the Agreement and so long as the insurance is reasonably available, for a period of five (5) years after final completion of the Project. For purposes of this Section, it is agreed that the required insurance is deemed reasonably available if: (a) any reputable insurer is willing to issue the insurance to such Design/Build Subcontractors; and (b) a significant number of such Design/Build subcontractors in the same practice in the same state in which the Project is located during the same period are able to obtain similar insurance. Such Design/Build Subcontractors shall prove to the reasonable satisfaction of Owner if at any time this insurance fails to be reasonably available.

(c) LBA may require additional insurance for Contractor. Contractor may also carry such other insurance as Contractor deems prudent (auto, physical damage, builder's risk insurance). All such insurance shall include a waiver of the insurer's rights of subrogation against Owner and LBA.

(d) LBA may require Contractor to submit payment and performance bonds covering the faithful performance of a Purchase Order and the payment of all obligations arising thereunder, in such form and with such sureties as are satisfactory to Owner and/or LBA.

B. **TERMS AND CONDITIONS OF INSURANCE**

(i) Within thirty (30) days of the date hereof but in no event later than Contractor's commencement of Work, Contractor shall file with LBA a valid/original "Certificate of Insurance" evidencing that all required insurance is in full force and effect. Contractor

shall file with LBA valid/original Certificates of Insurance prior to Contractor's renewal of each coverage described in this Exhibit "D". Contractor shall maintain current and valid Certificates of Insurance that shall be kept on file with LBA at all times during the term hereof and during the performance of Work pursuant to this Agreement. LBA will not process any invoices or applications for payment submitted by Contractor for Work performed unless LBA has valid/original Certificate(s) Insurance for Contractor and all subcontractors. Contractor shall not make any changes in or allow the required insurance coverages to lapse without first obtaining Owner's and/or LBA's prior written approval.

(ii) All policies for insurance shall be in form satisfactory to Owner and/or LBA and shall contain an endorsement providing that Owner and/or LBA must be given sixty (60) days' prior written notice of any cancellation, non-renewal or material change in the policy or coverage there under. Upon request Contractor shall furnish Owner and/or LBA with complete copies of the insurance policies required by this Exhibit "D".

(iii) Contractor shall add by endorsement to its policies of insurance, except for Workers' Compensation Insurance, LBA and its employees and agents, Owner and, if applicable, all beneficiaries thereunder, as additional insureds, using the following language:

LBA Realty LLC and its employees and agents, _____ (Ownership Entity) and all beneficiaries, if any are Additional Insureds jointly and/or severally regarding any coverage afforded by this policy with respect to services and/or materials performed, furnished or supplied on, for or to such properties. This insurance shall be primary with respect to any other insurance available to such additional insureds, and shall be endorsed in a manner that will prohibit the contractor's insurers from seeking contribution from such insurance of the additional insureds.

(iv) The failure to secure and maintain or add by endorsement LBA, its employees and agents, Owner and, if applicable, all beneficiaries thereunder, shall not act as a defense to the enforcement of the terms of this Agreement. Any such insurance policy shall apply separately to each insured against whom claim is made or suit is brought and shall contain no provision that excludes coverage of a claim made by one insured under the policy against another insured under the policy.

(v) Any insured loss covered by any property insurance or builders risk insurance applicable to the Work shall be adjusted with the Owner and made payable to the Owner, subject to any applicable mortgagee clause.

(vi) Show Certificate Holder as: (Ownership Entity)
c/o LBA Realty LLC
3347 Michelson Drive, Ste. 200
Irvine, CA 92612

C. **CONTRACTOR AND SUBCONTRACTOR INSURANCE LIMITS REQUIREMENTS**

	Division	Trade Description	Trade Number for Limits Required (See Attached)
1.	Site work	Earthwork	3
		Excavation	5
		Grading	2
		Paving	2
		Piling/Caisson	3
		Retention	4

	Division	Trade Description	Trade Number for Limits Required (See Attached)
2.	Concrete	Formwork	5
		Precasts	5
		Structural	5
3.	Masonry	Masonry	5
4.	Metal and Structural	Metal Deck	4
		Misc. Metals	2
		Structural Steel	5
5.	Carpentry	Millwork	2
		Rough Carpentry	2
		Wood Doors	2
6.	Moisture Protection	Caulking	3
		Damp proofing	3
		Roofing/Sheet Metal	5
		Waterproofing	3
7.	Doors, Windows and Glass	Curtain wall	5
		Glass, Glazing & Aluminum	3
		Hardware	1
		Hollow Metal Work	1
8.	Finishes	Acoustic	2
		Ceramic & Quarry	2
		Covering	2
		Lathe, Plaster & Drywall	2
		Resilient Floor	2
		Paint & Vinyl Wall	2
9.	Specialties	Access Flooring	1
		Partitions	1
		Toilet Accessories	1
10.	Equipment	Crane Operations	4
11.	Furnishings	Suppliers	1
12.	Special Construction	Asbestos Abatement	5
		Blasting	5
13.	Conveying Systems	Elevators	5
		Escalators	5
		Conveyers	3
		Dumbwaiters	3
14.	Mechanical	Fire Protection System	4
		Plumbing	4

	Division	Trade Description	Trade Number for Limits Required (See Attached)
15.	HVAC		5
16.	Electrical	Electrical	5
17.	Demolition	More Than 3 Stores 3 Stories or Less	10 5
18.	General Contractor	Major Project	50
19.	General Contractor	Performing Following Work: New construction Under 3 Stories and Less Than 100,000 Sq. Ft.; or Construction Contract Up to $5,000,000; or Renovation Less Than 15% of Existing Structure	10
20.	General Contractor	Performing Following Work: Any new renovation or repair work agreed by LBA and Owner to be of such size and scope to require special limits.	At Discretion of LBA/Owner

The following are the Limits of Liability required depending on the trade number of the Contractor:

Trade No.	Insurance Limits	
1.	$1,000,000 Each Occurrence $1,000,000 General Aggregate $1,000,000 Products & Completed Operations Aggregate	
2.	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate	
3.	$2,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $1,000,000 Umbrella Each Occurrence/Aggregate	OR
	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $2,000,000 Umbrella Each Occurrence/Aggregate	
4.	$2,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $2,000,000 Umbrella Each Occurrence/Aggregate	OR

Trade No.	Insurance Limits	
	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $3,000,000 Umbrella Each Occurrence/Aggregate	
5.	$2,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $3,000,000 Umbrella Each Occurrence/Aggregate	OR
	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $4,000,000 Umbrella Each Occurrence/Aggregate	
10.	$2,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $8,000,000 Umbrella Each Occurrence/Aggregate	OR
	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $9,000,000 Umbrella Each Occurrence/Aggregate	
50.	$2,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $49,000,000 Umbrella Each Occurrence/Aggregate	OR
	$1,000,000 Each Occurrence $2,000,000 General Aggregate $2,000,000 Products & Completed Operations Aggregate $50,000,000 Umbrella Each Occurrence/Aggregate	

Certificate of Insurance

Request Form

Please provide a complete Certificate of Insurance per the requirements set forth in this Purchase Order.

Provide a Certificate of Insurance showing the Ownership(s) Entity as follows: (showing the correct ownership entity or entities is critical). Also, please use this ownership entity for the purposes of any applicable conditional or unconditional waivers (this is the owner and checks will be issued from this entity as well).

(Ownership Entity) (Ownership Entity-please use this for Certificates of Insurance and Waivers, not LBA, Inc. or Layton Belling and Associates or LBA Realty)

c/o LBA Realty LLC
3347 Michelson Drive, Ste. 200
Irvine, CA 92612

Show Property as:

_____

1. Please reference the Ownership in the Certificate Holder Section.

2. Please reference the Ownership and Property in the Description of Operations Section.

3. An endorsement must be attached referencing the Property Address and Ownership for General Liability.

Send copies of Insurance Certificate to:

LBA Realty
3347 Michelson Drive, Ste. 200
Irvine, CA 92612
949-833-0440

NOTE: Please send invoices to:

(Insert admin e-mail address)

LBA Realty
3347 Michelson Drive, Ste. 200
Irvine, CA 92612

SCHEDULE C-2

[***]

SCHEDULE C-3

ESCROW AGREEMENT

This Tenant Construction Funds Escrow Agreement ("**Escrow Agreement**") is dated as of December ___, 2018, among BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC, a Delaware limited liability company ("**Landlord**"), ORCHARD THERAPEUTICS NORTH AMERICA, a California corporation ("**Tenant**"), and COMMONWEALTH LAND TITLE INSURANCE COMPANY ("**Escrow Holder**").

R E C I T A L S:

A.Substantially concurrently with the date of this Agreement, Landlord and Tenant have entered into that certain Single Tenant Commercial/Industrial Lease (the "**Lease**"), pursuant to which Tenant leases from Landlord the premises located at 800 Corporate Way, Fremont, CA (the "**Premises**"). Capitalized terms not otherwise defined herein shall have the meanings assigned to them in the Lease.

B.Pursuant to the Work Letter Agreement which is Exhibit C to the Lease, Tenant is to complete certain Tenant Improvements in and to the Premises and, pursuant to Section 5(h) of the Work Letter, Tenant is to deposit with Escrow Holder the sum of [***] (the "**Tenant Construction Funds**") to be held by Escrow Holder in a construction escrow account (the "**Construction Escrow**") as security for the benefit of Landlord until the full amount of the Tenant Construction Funds has been disbursed by Escrow Holder to Tenant as provided herein towards costs of completion of the Tenant Improvements for the Premises, [***] as shown on Tenant's initial Final Plans (but specifically excluding, without limitation, [***].

C.Landlord and Tenant desire to set forth, for and with Escrow Holder, the terms by which such Tenant Construction Funds are to be held and disbursed by Escrow Holder.

NOW THEREFORE, in consideration of the foregoing and of the mutual covenants hereinafter set forth, the parties hereto agree as follows:

1. **Appointment of Escrow Holder**. Landlord and Tenant do hereby appoint and designate Escrow Holder as the escrow holder for the Tenant Construction Funds for the purposes set forth herein, and Escrow Holder does hereby accept such appointment under the terms and conditions set forth herein.

2. **Establishment of Escrow Funds Account**.

   (A) **Construction [***] Account**. Escrow Holder shall place Tenant's deposit of the Tenant Construction Funds in the amount of [***].

   (B) **Escrow Funds**. Escrow Holder shall hold, subject to the terms and conditions hereof, the Tenant Construction Funds and such cash and such investments and reinvestments as may be permitted pursuant to Section 3 hereof (which, together with the income from such investments, are hereinafter referred to as the "**Escrow Funds**").

3. **Investment of Escrow Funds; Payment of Fees**.

   (A) **Investment**. During the term of this Escrow Agreement Escrow Holder shall invest and reinvest the Escrow Funds in a daily money market interest-bearing account as directed by Tenant.

   (B) **Fees**. The fee charged by Escrow Holder for services under this Escrow Agreement shall be [***].

   (C) **Liquidation**. Escrow Holder shall have the right to liquidate any investments held to provide funds necessary to make required payments under this Escrow Agreement. Escrow Holder in its capacity as escrow holder hereunder shall not have any liability for any loss sustained as a result of any investment made pursuant to the instructions of the parties hereto or as a result of any liquidation of any investment prior to its maturity or for the failure of the parties to give Escrow Holder instructions to invest or reinvest the Escrow Funds or any earnings thereon.

4. **Disposition and Termination**.

(A) **Disbursement of the Escrow Funds to Tenant**. Escrow Holder shall disburse the Tenant Construction Funds from the Escrow Funds [***].

(B) **Final Disbursement; Outside Termination Date**. If Tenant shall fail to expend all of the Tenant Construction Funds on or before [***] (the "**Outside Termination Date**"), Escrow Holder shall disburse the balance of the Tenant Construction Funds and all interest accrued thereon to Tenant after deducting any remaining charges payable to Escrow Holder, whereupon this Agreement and the Escrow shall terminate and neither party shall have any further rights or obligations under this Agreement.

(C) **Dispute Resolution**. If [***], then Landlord and Tenant agree to negotiate in good faith to resolve any such dispute; provided, however, nothing contained in this Section 4(C) shall prevent either Tenant or Landlord from exercising such other rights and/or remedies to the extent such party reasonably deems such action necessary to preserve its rights or the status quo pending such resolution. If the negotiations do not resolve the dispute to the reasonable satisfaction of both parties within a period of thirty (30) days after Landlord first notifies Tenant and Escrow Holder of the dispute referenced in this Section (the "**Executive Discussion Period**"), then Tenant and Landlord shall meet, within thirty (30) days following the expiration of the Executive Discussion Period, for one day with an impartial mediator and consider dispute resolution alternatives other than litigation. If an alternative method of dispute resolution is not agreed upon within thirty (30) days after the one day mediation, either Tenant or Landlord may initiate binding arbitration as set forth below. This procedure shall be a prerequisite before taking any additional action hereunder. Tenant and Landlord hereby acknowledge and agree that such mediation shall be deemed to be in the nature of settlement discussions and that neither the fact that such discussions took place, nor any statement or conduct of any participant in such discussions shall be admissible into evidence in any subsequent litigation or in any arbitration or other dispute resolution proceeding involving the parties. It is further understood and agreed that any disclosure in any form, including oral, by any person participating in such mediation shall not operate as a waiver of any privilege, including work product or attorney-client privilege, applicable to the subject matter thereof. All applicable statutes of limitations shall be deemed to be tolled from the commencement of any negotiation, dispute resolution, settlement discussions or mediation hereunder through its conclusion or termination. Arbitration shall be held in Orange County, California and shall be conducted in accordance with the then-prevailing rules of the American Arbitration Association by one (1) arbitrator appointed by Tenant, one (1) arbitrator appointed by Landlord and one (1) arbitrator jointly selected by the two (2) arbitrators chosen by Tenant and Landlord. A decision or award of the arbitrator shall be final and may be entered as a final judgment in any court, state or federal, having jurisdiction. The costs of the mediation and/or arbitration shall be shared equally by Landlord and Tenant. Pending resolution of any such dispute Escrow Holder shall continue to hold the Tenant Construction Funds as provided in this Escrow Agreement.

(D) **Termination**. Upon disbursement by Escrow Holder of all of the Tenant Construction Funds and interest accrued thereon, net of Escrow Holder's accrued and unpaid fees, if any, this Escrow Agreement shall terminate, subject to the provisions of Section 7 hereof.

5. **Escrow Holder Duties and Limitations**.

(A) The duties and responsibilities of Escrow Holder hereunder shall be determined solely by the express provisions of this Escrow Agreement and no other or further duties or responsibilities shall be implied. Escrow Holder shall not have any liability under, nor duty to inquire into, the terms and provisions of any agreement or instructions, other than outlined in this Escrow Agreement, the only role of Escrow Holder being to hold the Escrow Funds as provided herein, [***].

(B) Escrow Holder may rely and shall be protected in acting or refraining from acting upon any written notice, instruction or request furnished to it hereunder and believed by it to be genuine and to have been signed or presented by the proper party or parties. Escrow Holder shall be under no duty to inquire into or investigate the validity, accuracy or content of any such document. Escrow Holder shall have no duty to solicit any payments that may be due it hereunder.

(C) Provided that Escrow Holder has deposited the Escrow Funds in an investment account in accordance with the provisions of Section 3(A) hereof, Escrow Holder shall not be liable and shall be held harmless for (a) any losses of the Escrow Funds caused by a failure of any banking institution with whom the Escrow Funds have been deposited, and (b) the performance of the investment and/or institution in which the Escrow Fund is deposited.

(D) Escrow Holder shall not be liable for any action taken or omitted by it in good faith unless a court of competent jurisdiction determines that Escrow Holder's willful misconduct was the primary cause of any loss to Landlord or Tenant. In the administration of the Tenant Construction Funds hereunder, Escrow Holder may execute any of its powers and perform its duties hereunder directly or through agents or attorneys and may consult with counsel, accountants and other skilled persons to be selected and retained by it. Escrow Holder shall not be liable for anything done, suffered or omitted in good faith by it in accordance with the advice or opinion of any such counsel, accountants or other skilled persons.

(E) Escrow Holder may resign and be discharged from its duties or obligations hereunder by giving notice in writing of such resignation specifying a date when such resignation shall take effect.

(F) If Escrow Holder shall be uncertain as to its duties or rights hereunder or shall receive instructions, claims or demands from any party hereto which, in its opinion, conflict with any of the provisions of this Escrow Agreement, it shall be entitled to refrain from taking any action and its sole obligation shall be to keep safely all property held in escrow until it shall be directed otherwise in writing by all of the other parties hereto, by a final order or judgment of a court of competent jurisdiction or by arbitration as provided in this Escrow Agreement.

6. **Payment of Escrow Fees**. Notwithstanding anything to the contrary contained herein, the parties hereby agree that all income from the investments and reinvestments of the Escrow Funds as described in Section 3 hereof, shall constitute the property of Tenant. Tenant shall be responsible for the payment of Escrow Holder’s fees and costs for acting as Escrow Holder pursuant to the terms of this Escrow Agreement.

7. **Indemnification**. In the event of any suit or claim made against Escrow Holder by any party to this Escrow Agreement, Landlord and Tenant jointly and severally shall indemnify, defend and save harmless Escrow Holder from all loss, liability or expense (including the fees and expenses of in house or outside counsel) arising out of or in connection with (i) its execution and performance of this Agreement, except to the extent that such loss, liability or expense is due to the gross negligence or willful misconduct of Escrow Holder, or (ii) its following any written instructions or other written directions executed by Landlord and Tenant, except to the extent that its following any such instruction or direction is contrary to the terms hereof. Anything in this Escrow Agreement to the contrary notwithstanding, in no event shall Escrow Holder be liable for special, indirect or consequential loss or damage of any kind whatsoever (including but not limited to lost profits). The parties hereto acknowledge that the foregoing indemnities shall survive the resignation or removal of Escrow Holder or the termination of this Escrow Agreement.

8. **Tax Identification Numbers**. Each party hereto, except Escrow Holder, shall, in the notice section of this Agreement, provide Escrow Holder with its Tax Identification Number (TIN) as assigned by the Internal Revenue Service. All interest or other income earned under this Escrow Agreement shall be allocated and paid as provided herein and reported by the recipient to the Internal Revenue Service as having been so allocated and paid.

9. **Notices**. All notices and communications hereunder shall be in writing and shall be deemed to be duly given if sent by (i) overnight delivery by reputable carrier, or (ii) email via PDF with original in mail to follow, as follows:

If to the Escrow Holder:

Commonwealth Land Title Company
888 S. Figueroa Street, Suite 2100
Los Angeles, CA 90017
Direct Dial: [***]
Attention: [***]
Telephone: [***]
Email: [***]

If to Landlord:

c/o LBA Realty LLC
3347 Michelson Drive, Suite 200
Irvine, California 92612
Attn: SVP – Operations
Telephone: [***]

E-mail: [***]

If to Tenant:

Orchard Therapeutics North America
1360 O'Brien Avenue
Menlo Park, California 94025
Attn: [***]
Telephone: [***]
E-mail: [***]

or at such other address as any of the above may have furnished to the other parties in writing by registered mail, return receipt requested and any such notice or communication given in the manner specified in this Section 9 shall be deemed to have been given as of the date so mailed except with respect to the Escrow Holder as to which such notice or communication shall be deemed to have been given on the date received by the Escrow Holder.

10. **Miscellaneous**.

(A) The provisions of this Escrow Agreement may be waived, altered, amended or supplemented, in whole or in part, only in writing signed by all of the parties hereto.

(B) Neither this Escrow Agreement nor any right or interest hereunder may be assigned in whole or in part by any party without the prior consent of the other parties.

(C) This Escrow Agreement may be executed in one or more counterparts, each of which shall be deemed an original, but all of which together shall constitute one and the same instrument. All signatures of the parties to this Agreement may be transmitted by facsimile, and such facsimile will, for all purposes, be deemed to be the original signature of such party whose signature it reproduces and will be binding upon such party.

(D) This Escrow Agreement shall be governed by and construed in accordance with the laws of California without regard to its principles of conflicts of laws.

(E) In the event that any party to this Escrow Agreement is unable to perform its obligations under the terms of this Escrow Agreement because of acts of God, strikes, equipment or transmission failure or damage reasonably beyond its control, or other cause reasonably beyond its control (but specifically excluding financial inability), such party shall not be liable for damages to the other parties for any unforeseeable damages resulting from such failure to perform or otherwise from such causes. Performance under this Escrow Agreement shall resume when the affected party is able to perform substantially that party's duties.

[The remainder of this page is intentionally left blank]

IN WITNESS WHEREOF, the parties hereto have executed this Escrow Agreement on the date and year first above written.

LANDLORD:

BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC, a Delaware limited liability company

By: _____
Its: Authorized Signatory

TENANT:

ORCHARD THERAPEUTICS NORTH AMERICA, a California corporation

By: _____
Name: _____
Title: _____

ESCROW HOLDER:

COMMONWEALTH LAND TITLE INSURANCE COMPANY

By: _____
Name: _____
Title: _____

[***]

Schedule C-3
1

*** Confidential Treatment Requested ***

EXHIBIT D

NOTICE OF LEASE TERM DATES

Date:

To:

Re:_____ dated _____ ("Lease") by and between _____, a _____ ("Landlord"), and _____, a _____ ("Tenant") for the premises commonly known as, _____("Premises").

Dear :

In accordance with the above-referenced Lease, we wish to advise and/or confirm as follows:

- That Tenant has accepted and is in possession of the Premises and acknowledges the following:
  - Term of the Lease:
  - Commencement Date:
  - Expiration Date:
  - Rentable Square Feet:
  -
- That in accordance with the Lease, rental payments will/has commence(d) on _____ and rent is payable in accordance with the following schedule:

Months	Monthly Base Rent
00/00/0000 – 00/00/0000	$00,000.00
00/00/0000 – 00/00/0000	$00,000.00
00/00/0000 – 00/00/0000	$00,000.00

- Rent is due and payable in advance on the first day of each and every month during the Term of the Lease.
- Your rent checks should be made payable to:

ACCEPTED AND AGREED

TENANT:

_____

a, _____

By: _____

Print Name: _____

Its: _____

LANDLORD:

_____

a, _____

By: _____

EXHIBIT E

ESTOPPEL CERTIFICATE

The undersigned ("**Tenant**") hereby certifies to ("**Landlord**"), and , as follows:

1. Attached hereto is a true, correct and complete copy of that certain Lease dated _____, between Landlord and Tenant (the "**Lease**"), for the premises commonly known as _____ (the "**Premises**"). The Lease is now in full force and effect and has not been amended, modified or supplemented, except as set forth in Section 6 below.

2. The term of the Lease commenced on _____, __.

3. The term of the Lease is currently scheduled to expire on _____, __.

4. Tenant has no option to renew or extend the Term of the Lease except: .

5. Tenant has no preferential right to purchase the Premises or any portion of the Building/Premises except: _____.

6. The Lease has: (Initial One)
( ) not been amended, modified, supplemented, extended, renewed or assigned.
( ) been amended, modified, supplemented, extended, renewed or assigned by the following described agreements, copies of which are attached hereto: .

7. Tenant has accepted and is now in possession of the Premises and has not sublet, assigned or encumbered the Lease, the Premises or any portion thereof except as follows: .

8. The current Base Rent is $_____; and current monthly parking charges are $_____.

9. The amount of security deposit (if any) is $_____. No other security deposits have been made.

10. All rental payments payable by Tenant have been paid in full as of the date hereof. No rent under the Lease has been paid for more than thirty (30) days in advance of its due date.

11. All work required to be performed by Landlord under the Lease has been completed and has been accepted by Tenant, and all tenant improvement allowances have been paid in full except _____.

12. As of the date hereof, Tenant is not aware of any defaults on the part of Landlord under the Lease except _____.

13. As of the date hereof, there are no defaults on the part of Tenant under the Lease.

14. Tenant has no defense as to its obligations under the Lease and claims no set-off or counterclaim against Landlord.

15. Tenant has no right to any concession (rental or otherwise) or similar compensation in connection with renting the space it occupies, except as expressly provided in the Lease.

16. All insurance required of Tenant under the Lease has been provided by Tenant and all premiums have been paid.

17. There has not been filed by or against Tenant a petition in bankruptcy, voluntary or otherwise, any assignment for the benefit of creditors, any petition seeking reorganization or arrangement under the bankruptcy laws of the United States or any state thereof, or any other action brought pursuant to such bankruptcy laws with respect to Tenant.

18. Tenant pays rent due Landlord under the Lease to Landlord and does not have any knowledge of any other person who has any right to such rents by collateral assignment or otherwise.

The foregoing certification is made with the knowledge that _____ is about to [fund a loan to Landlord or purchase the Building from Landlord], and that _____ is relying upon the representations herein made in [funding such loan or purchasing the Building].

Dated: _____

"TENANT"

By: _____
Print Name: _____
Its: _____

EXHIBIT F

ENVIRONMENTAL QUESTIONNAIRE AND DISCLOSURE STATEMENT

The purpose of this form is to obtain information regarding the use or proposed use of hazardous materials at the premises. Prospective tenants should answer the questions in light of their proposed operations at the premises. Existing tenants should answer the questions as they relate to ongoing operations at the premises and should update any information previously submitted. If additional space is needed to answer the questions, you may attach separate sheets of paper to this form.

Your cooperation in this matter is appreciated.

1. GENERAL INFORMATION

Name of Responding Company: Orchard Therapeutics North America

Check the Applicable Status: Prospective Tenant XExisting Tenant _____

Mailing Address: [***]

Contact Person and Title: [***]

Telephone Number: [***]

Address of Leased Premises: 800 Corporate Way Fremont, CA 94539

Length of Term: 138 Months

Describe the proposed operations to take place on the premises, including principal products manufactured or services to be conducted. Existing tenants should describe any proposed changes to ongoing operations.

[***]

2. STORAGE OF HAZARDOUS MATERIALS

2.1 Will any hazardous materials be used or stored on-site?

Wastes [***]

Chemical Products [***]

2.2 Attach a list of any hazardous materials to be used or stored, the quantities that will be on-site at any given time, and the location and method of storage (e.g., 55-gallon drums on concrete pad).

[***]

3. STORAGE TANKS AND SUMPS

3.1 Is any above or below ground storage of gasoline, diesel or other hazardous substances in tanks or sumps proposed or currently conducted at the premises?

[***]

3.2 Have any of the tanks or sumps been inspected or tested for leakage?

[***]

3.3 Have any spills or leaks occurred from such tanks or sumps?

[***]

3.4 Were any regulatory agencies notified of the spill or leak?

[***]

3.5 Have any underground storage tanks or sumps been taken out of service or removed?

[***]

4. SPILLS

4.1 During the past year, have any spills occurred at the premises?

[***]

4.2 Were any agencies notified in connection with such spills?

[***]

4.3 Were any clean-up actions undertaken in connection with the spills?

[***]

5. WASTE MANAGEMENT

5.1 Has your company been issued an EPA Hazardous Waste Generator I.D. Number?

[***]

5.2 Has your company filed a biennial report as a hazardous waste generator?

[***]

5.3 Attach a list of the hazardous wastes, if any, generated or to be generated at the premises, its hazard class and the quantity generated on a monthly basis.

[***]

5.4 Describe the method(s) of disposal for each waste. Indicate where and how often disposal will take place.

[***]

5.5 Indicate the name of the person(s) responsible for maintaining copies of hazardous waste manifests completed for off-site shipments of hazardous waste.

[***]

5.6 Is any treatment of processing of hazardous wastes currently conducted or proposed to be conducted at the premises:

[***]

5.7 Attach copies of any hazardous waste permits or licenses issued to your company with respect to its operations at the premises.

6. WASTEWATER TREATMENT/DISCHARGE

6.1 Do you discharge wastewater to:

[***]

6.2 Is your wastewater treated before discharge?

[***]

6.3 Attach copies of any wastewater discharge permits issued to your company with respect to its operations at the premises.

7. AIR DISCHARGES

7.1 Do you have any filtration systems or stacks that discharge into the air?

[***]

7.2 Do you operate any of the following types of equipment or any other equipment requiring an air emissions permit?

[***]

7.3 Are air emissions from your operations monitored?

[***]

If so, indicate the frequency of monitoring and a description of the monitoring results.

[***]

7.4 Attach copies of any air emissions permits pertaining to your operations at the premises.

8. HAZARDOUS MATERIALS DISCLOSURES

8.1 Does your company handle hazardous materials in a quantity equal to or exceeding an aggregate of 500 pounds, 55 gallons, or 200 cubic feet per month?

[***]

8.2 Has your company prepared a hazardous materials management plan pursuant to any applicable requirements of a local fire department or governmental agency?

[***]

8.3 Has your company adopted any voluntary environmental, health or safety program?

[***]

9. ENFORCEMENT ACTIONS, COMPLAINTS

9.1 Has your company ever been subject to any agency enforcement actions, administrative orders, or consent decrees?

[***]

9.2 Has your company ever received requests for information, notice or demand letters, or any other inquiries regarding its operations?

[***]

9.3 Have there ever been, or are there now pending, any lawsuits against the company regarding any environmental or health and safety concerns?

[***]

9.4 Has an environmental audit ever been conducted at your company's current facility?

[***]

Tenant: Orchard Therapeutics NA
By: [***]

EXHIBIT G

FORM OF LETTER OF CREDIT

_____

L/C DRAFT LANGUAGE

IRREVOCABLE STANDBY LETTER OF CREDIT NUMBER _____

ISSUE DATE: _____

ISSUING BANK:
[***]
[***]
[***]
[***]

BENEFICIARY:
BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC
c/o LBA Realty LLC
3347 Michelson Drive, Suite 200
Irvine, California 92612
Attn: Mike Memoly

APPLICANT:
ORCHARD THERAPEUTICS NORTH AMERICA
1118 CHESS DRIVE SUITE A
FOSTER CITY CA 94404

AMOUNT: [***]

EXPIRATION DATE: _____

PLACE OF EXPIRATION: ISSUING BANK'S COUNTERS AT ITS ABOVE ADDRESS

DEAR SIR/MADAM:

WE HEREBY ESTABLISH OUR IRREVOCABLE STANDBY LETTER OF CREDIT NO. SVBSF_____ IN YOUR FAVOR AVAILABLE BY PAYMENT AGAINST YOUR PRESENTATION TO US OF THE FOLLOWING DOCUMENT:

1. BENEFICIARY'S SIGNED AND DATED STATEMENT STATING AS FOLLOWS:

"AN EVENT OF DEFAULT (AS DEFINED IN THE LEASE) HAS OCCURRED UNDER THAT CERTAIN LEASE AGREEMENT BETWEEN _____, AS TENANT, AND _____ AS LANDLORD".

PARTIAL DRAWS AND MULTIPLE PRESENTATIONS ARE ALLOWED.

THIS LETTER OF CREDIT SHALL BE AUTOMATICALLY EXTENDED FOR AN ADDITIONAL PERIOD OF ONE YEAR, WITHOUT AMENDMENT, FROM THE PRESENT OR EACH FUTURE EXPIRATION DATE UNLESS AT LEAST NINETY (90) DAYS PRIOR TO THE THEN CURRENT EXPIRATION DATE WE SEND TO YOU A NOTICE BY REGISTERED OR CERTIFIED MAIL OR OVERNIGHT COURIER SERVICE AT THE ABOVE ADDRESS THAT THIS LETTER OF CREDIT WILL NOT BE EXTENDED BEYOND THE THEN CURRENT EXPIRATION DATE. IN NO EVENT SHALL THIS LETTER OF CREDIT BE AUTOMATICALLY EXTENDED BEYOND _____. IN THE EVENT WE SEND SUCH NOTICE OF NON-EXTENSION, YOU MAY DRAW HEREUNDER BY YOUR PRESENTATION TO US OF YOUR SIGNED AND DATED STATEMENT STATING THAT YOU HAVE RECEIVED A NON-EXTENSION NOTICE FROM [***] IN RESPECT OF LETTER OF CREDIT NO. SVBSF _____, YOU ARE DRAWING ON SUCH

[***]

APPLICANT'S SIGNATURE(s) DATE

LETTER OF CREDIT FOR US$_____, AND YOU HAVE NOT RECEIVED A REPLACEMENT LETTER OF CREDIT ACCEPTABLE TO YOU.

ALL DEMANDS FOR PAYMENT SHALL BE MADE BY PRESENTATION OF THE REQUIRED DOCUMENTS ON A BUSINESS DAY AT OUR OFFICE (THE "BANK'S OFFICE") AT: [***].

FACSIMILE PRESENTATIONS ARE ALSO PERMITTED. SHOULD BENEFICIARY WISH TO MAKE A PRESENTATION UNDER THIS LETTER OF CREDIT ENTIRELY BY FACSIMILE TRANSMISSION IT NEED NOT TRANSMIT THE ORIGINAL OF THIS LETTER OF CREDIT AND AMENDMENTS, IF ANY. EACH FACSIMILE TRANSMISSION SHALL BE MADE AT: [***]; AND UNDER CONTEMPORANEOUS TELEPHONE ADVICE TO: [***]. ABSENCE OF THE AFORESAID TELEPHONE ADVICE SHALL NOT AFFECT OUR OBLIGATION TO HONOR ANY DRAW REQUEST.

THIS LETTER OF CREDIT IS TRANSFERABLE IN WHOLE BUT NOT IN PART ONE OR MORE TIMES, BUT IN EACH INSTANCE ONLY TO A SINGLE BENEFICIARY AS TRANSFEREE AND FOR THE THEN AVAILABLE AMOUNT, ASSUMING SUCH TRANSFER TO SUCH TRANSFEREE WOULD BE IN COMPLIANCE WITH THEN APPLICABLE LAW AND REGULATION, INCLUDING BUT NOT LIMITED TO THE REGULATIONS OF THE U.S. DEPARTMENT OF TREASURY AND U.S. DEPARTMENT OF COMMERCE. AT THE TIME OF TRANSFER, THE ORIGINAL LETTER OF CREDIT AND ORIGINALS OR COPIES OF ALL AMENDMENTS, IF ANY, TO THIS LETTER OF CREDIT MUST BE SURRENDERED TO US AT OUR ADDRESS INDICATED IN THIS LETTER OF CREDIT TOGETHER WITH OUR TRANSFER FORM ATTACHED HERETO AS EXHIBIT A DULY EXECUTED. THE CORRECTNESS OF THE SIGNATURE AND TITLE OF THE PERSON SIGNING THE TRANSFER FORM MUST BE VERIFIED BY BENEFICIARY'S BANK. APPLICANT SHALL PAY OUR TRANSFER FEE OF ¼ OF 1% OF THE TRANSFER AMOUNT (MINIMUM US$250.00) UNDER THIS LETTER OF CREDIT. EACH TRANSFER SHALL BE EVIDENCED BY EITHER (1) OUR ENDORSEMENT ON THE REVERSE OF THE LETTER OF CREDIT AND WE SHALL FORWARD THE ORIGINAL OF THE LETTER OF CREDIT SO ENDORSED TO THE TRANSFEREE OR (2) OUR ISSUING A REPLACEMENT LETTER OF CREDIT TO THE TRANSFEREE ON SUBSTANTIALLY THE SAME TERMS AND CONDITIONS AS THE TRANSFERRED LETTER OF CREDIT (IN WHICH EVENT THE TRANSFERRED LETTER OF CREDIT SHALL HAVE NO FURTHER EFFECT).

IF ANY INSTRUCTIONS ACCOMPANYING A DRAWING UNDER THIS LETTER OF CREDIT REQUEST THAT PAYMENT IS TO BE MADE BY TRANSFER TO YOUR ACCOUNT WITH ANOTHER BANK, WE WILL ONLY EFFECT SUCH PAYMENT BY FED WIRE TO A U.S. REGULATED BANK, AND WE AND/OR SUCH OTHER BANK MAY RELY ON AN ACCOUNT NUMBER SPECIFIED IN SUCH INSTRUCTIONS EVEN IF THE NUMBER IDENTIFIES A PERSON OR ENTITY DIFFERENT FROM THE INTENDED PAYEE.

THIS LETTER OF CREDIT IS SUBJECT TO THE INTERNATIONAL STANDBY PRACTICES (ISP98), INTERNATIONAL CHAMBER OF COMMERCE, PUBLICATION NO. 590.

_____ _____

AUTHORIZED SIGNATURE AUTHORIZED SIGNATURE

[***]

APPLICANT'S SIGNATURE(s) DATE

IRREVOCABLE STANDBY LETTER OF CREDIT NUMBER _____

EXHIBIT A

FORM OF TRANSFER FORM

DATE: _____

TO: [***]
[***] RE: IRREVOCABLE STANDBY LETTER OF CREDIT
[***] [***]
[***] [***]

STANDBY LETTERS OF CREDIT L/C AMOUNT: _____

GENTLEMEN:

FOR VALUE RECEIVED, THE UNDERSIGNED BENEFICIARY HEREBY IRREVOCABLY TRANSFERS TO:

_____
(NAME OF TRANSFEREE)

_____
(ADDRESS)

ALL RIGHTS OF THE UNDERSIGNED BENEFICIARY TO DRAW UNDER THE ABOVE LETTER OF CREDIT UP TO ITS AVAILABLE AMOUNT AS SHOWN ABOVE AS OF THE DATE OF THIS TRANSFER.

BY THIS TRANSFER, ALL RIGHTS OF THE UNDERSIGNED BENEFICIARY IN SUCH LETTER OF CREDIT ARE TRANSFERRED TO THE TRANSFEREE. TRANSFEREE SHALL HAVE THE SOLE RIGHTS AS BENEFICIARY THEREOF, INCLUDING SOLE RIGHTS RELATING TO ANY AMENDMENTS, WHETHER INCREASES OR EXTENSIONS OR OTHER AMENDMENTS, AND WHETHER NOW EXISTING OR HEREAFTER MADE. ALL AMENDMENTS ARE TO BE ADVISED DIRECTLY TO THE TRANSFEREE WITHOUT NECESSITY OF ANY CONSENT OF OR NOTICE TO THE UNDERSIGNED BENEFICIARY.

THE ORIGINAL OF SUCH LETTER OF CREDIT IS RETURNED HEREWITH, AND WE ASK YOU TO EITHER (1) ENDORSE THE TRANSFER ON THE REVERSE THEREOF, AND FORWARD IT DIRECTLY TO THE TRANSFEREE WITH YOUR CUSTOMARY NOTICE OF TRANSFER, OR (2) ISSUE A REPLACEMENT LETTER OF CREDIT TO THE TRANSFEREE ON SUBSTANTIALLY THE SAME TERMS AND CONDITIONS AS THE TRANSFERRED LETTER OF CREDIT (IN WHICH EVENT THE TRANSFERRED LETTER OF CREDIT SHALL HAVE NO FURTHER EFFECT).

SINCERELY,

_____
(BENEFICIARY'S NAME)

_____
(SIGNATURE OF BENEFICIARY)

_____
(NAME AND TITLE)

[***]

APPLICANT'S SIGNATURE(s) DATE

SIGNATURE AUTHENTICATED

The name(s), title(s), and signature(s) conform to that/those on file with us for the company and the signature(s) is/are authorized to execute this instrument.

_____

(Name of Bank)

_____

(Address of Bank)

_____

(City, State, ZIP Code)

_____

(Authorized Name and Title)

_____

(Authorized Signature)

_____

(Telephone number)

[***]

APPLICANT'S SIGNATURE(s) DATE

EXTENSION OPTION

RIDER NO. 1 TO LEASE

This Rider No. 1 is made and entered into by and between BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC, a Delaware limited liability company ("**Landlord**"), and ORCHARD THERAPEUTICS NORTH AMERICA, a California corporation ("**Tenant**"), as of the day and year of the Lease between Landlord and Tenant to which this Rider is attached. Landlord and Tenant hereby agree that, notwithstanding anything contained in the Lease to the contrary, the provisions set forth below shall be deemed to be part of the Lease and shall supersede any inconsistent provisions of the Lease. All references in the Lease and in this Rider to the "Lease" shall be construed to mean the Lease (and all Exhibits and Riders attached thereto), as amended and supplemented by this Rider. All capitalized terms not defined in this Rider shall have the same meaning as set forth in the Lease.

1. Landlord hereby grants to Tenant one (1) option ("**Extension Option**") to extend the Term of the Lease for one additional period of ten (10) years (the "**Option Term**"), on the same terms, covenants and conditions as provided for in the Lease during the initial Term, except for the Monthly Base Rent, which shall initially be equal to the "fair market rental rate" for the Premises for the Option Term as defined and determined in accordance with the provisions of the Fair Market Rental Rate Rider attached to the Lease as Rider No. 2, subject to fair market annual rent adjustments during the Option Term. Such fair market rental rate shall be determined in accordance with the Fair Market Rental Rate Rider attached to the Lease as Rider No. 2.

2. An Extension Option must be exercised, if at all, by written notice ("**Extension Notice**") delivered by Tenant to Landlord no sooner than that date which is fifteen (15) months and no later than that date which is twelve (12) months prior to the expiration of the then current Term of the Lease. Provided Tenant has properly and timely exercised the Extension Option, the then current Term of the Lease shall be extended by the Option Term, and all terms, covenants and conditions of the Lease shall remain unmodified and in full force and effect, except that the Monthly Base Rent shall be as set forth above, and except that the number of remaining Extension Options (if any) shall be reduced by one.

3. The Extension Option is personal to (i) the original Tenant executing this Lease, or (ii) a Permitted Transferee, and may be exercised only by the original Tenant executing this Lease (or such Permitted Transferee) while occupying at least fifty percent (50%) of the Premises, and may not be exercised or be assigned, voluntarily or involuntarily, by any person or entity other than the original Tenant executing this Lease or such Permitted Transferee. The Extension Option granted to Tenant under this Lease is not assignable separate and apart from this Lease, nor may such Extension Option be separated from this Lease in any manner, either by reservation or otherwise. Tenant will have no right to exercise any Extension Option, notwithstanding any provision of the grant of the Extension Option to the contrary, and Tenant's exercise of such Extension Option may be nullified by Landlord and deemed of no further force or effect, if (i) a Default exists as of Tenant's exercise of the Extension Option in question or (ii) Tenant has sublet all or more than fifty percent (50%) of the Premises except pursuant to a Permitted Transfer. The Extension Option granted to Tenant is hereby deemed an economic term which Landlord, in its sole and absolute discretion, may or may not offer in conjunction with any future extensions of the Term.

FAIR MARKET RENTAL RATE

RIDER NO. 2 TO LEASE

This Rider No. 2 is made and entered into by and between BPP PACIFIC INDUSTRIAL CA NON-REIT OWNER 2 LLC, a Delaware limited liability company ("**Landlord**"), and ORCHARD THERAPEUTICS NORTH AMERICA, a California corporation ("**Tenant**"), as of the day and year of the Lease between Landlord and Tenant to which this Rider is attached. Landlord and Tenant hereby agree that, notwithstanding anything contained in the Lease to the contrary, the provisions set forth below shall be deemed to be part of the Lease and shall supersede any inconsistent provisions of the Lease. All references in the Lease and in this Rider to the "Lease" shall be construed to mean the Lease (and all Exhibits and Riders attached thereto), as amended and supplemented by this Rider. All capitalized terms not defined in this Rider shall have the same meaning as set forth in the Lease.

1. The term "**fair market rental rate**" as used in this Rider and any Rider attached to the Lease means the annual amount per square foot, projected for each year of the Option Term (including annual adjustments), that a willing, non-equity tenant (excluding sublease and assignment transactions) would pay, and a willing landlord of a comparable quality research and development building located in the Fremont, California area would accept, in an arm's length transaction, for space of comparable size, quality and ceiling height as the Premises, taking into account the age, quality and layout of the existing improvements in the Premises, the value of the portion of the Tenant Improvements paid for by Landlord via the Allowance [***], and taking into account all relevant factors, including items that professional real estate brokers or professional real estate appraisers customarily consider, including, but not limited to, rental rates, space availability, tenant size, parking charges, if any, and any other lease considerations, if any, then being charged or granted by Landlord or the lessors of such similar buildings, but excluding the value of any improvements paid for by Tenant (including, without limitation, value of the Tenant Improvements exclusive of any portion thereof paid for by the Allowance). All economic terms other than Monthly Base Rent, such as tenant improvement allowance amounts, if any, operating expense allowances, parking charges, etc., will be established by Landlord and will be factored into the determination of the fair market rental rate for the Option Term. Accordingly, the fair market rental rate will be an effective rate, not specifically including, but accounting for, the appropriate economic considerations described above.

2. Landlord shall provide written notice of Landlord's determination of the fair market rental rate not later than sixty (60) days after the day upon which Tenant timely exercises the right giving rise to the necessity for such fair market rental rate determination. Tenant shall have thirty (30) days ("**Tenant's Review Period**") after receipt of Landlord's notice of the fair market rental rate within which to (i) accept such fair market rental rate, (ii) object thereto in writing or (iii) rescind its Extension Notice. Failure of Tenant to so rescind its Extension Notice or to so object to the fair market rental rate submitted by Landlord in writing within Tenant's Review Period shall conclusively be deemed Tenant's approval and acceptance thereof. If within Tenant's Review Period Tenant objects to or is deemed to have disapproved the fair market rental rate submitted by Landlord, Landlord and Tenant will meet together with their respective brokers to present and discuss their individual determinations of the fair market rental rate for the Premises under the parameters set forth in Paragraph 1 above and shall diligently and in good faith attempt to negotiate a rental rate on the basis of such individual determinations. Such meeting shall occur no later than ten (10) days after the expiration of Tenant's Review Period. The parties shall each provide the other with such supporting information and documentation as they deem appropriate. At such meeting if Landlord and Tenant are unable to agree upon the fair market rental rate, they shall each submit to the other their respective best and final offer as to the fair market rental rate. If Landlord and Tenant fail to reach agreement on such fair market rental rate within five (5) business days following such a meeting (the "**Outside Agreement Date**"), Tenant's Extension Option will be deemed null and void unless Tenant demands appraisal, in which event each party's determination shall be submitted to appraisal in accordance with the provisions of Section 3 below.

3. (a) Landlord and Tenant shall each appoint one (1) independent appraiser who shall by profession be an M.A.I. certified real estate appraiser who shall have been active over the five (5) year period ending on the date of such appointment in the leasing of commercial (including office) properties in the California Commerce Center in the Baldwin Park, California area. The determination of the appraisers shall be limited solely to the issue of whether Landlord's or Tenant's last proposed (as of the Outside Agreement Date) best and final fair market rental rate for the Premises is the closest to the actual fair market rental rate for the Premises as determined by the appraisers, taking into account the requirements specified in Section 1 above. Each such appraiser shall be appointed within ten (10) business days after the Outside Agreement Date.

(b) The two (2) appraisers so appointed shall within ten (10) business days after the date of the appointment of the last appointed appraiser agree upon and appoint a third appraiser who shall be qualified under the same criteria set forth hereinabove for qualification of the initial two (2) appraisers.

(c) The three (3) appraisers shall within ten (10) business days after the appointment of the third appraiser reach a decision as to whether the parties shall use Landlord's or Tenant's submitted best and

final fair market rental rate, and shall notify Landlord and Tenant thereof. During such ten (10) business day period, Landlord and Tenant may submit to the appraisers such information and documentation to support their respective positions as they shall deem reasonably relevant and Landlord and Tenant may each appear before the appraisers jointly to question and respond to questions from the appraisers.

(d) The decision of the majority of the three (3) appraisers shall be binding upon Landlord and Tenant and neither party shall have the right to reject the decision or to undo the exercise of the applicable Option. If either Landlord or Tenant fails to appoint an appraiser within the time period specified in Section 3(a) hereinabove, the appraiser appointed by one of them shall within ten (10) business days following the date on which the party failing to appoint an appraiser could have last appointed such appraiser reach a decision based upon the same procedures as set forth above (i.e., by selecting either Landlord's or Tenant's submitted best and final fair market rental rate), and shall notify Landlord and Tenant thereof, and such appraiser's decision shall be binding upon Landlord and Tenant and neither party shall have the right to reject the decision or to undo the exercise of the applicable Option.

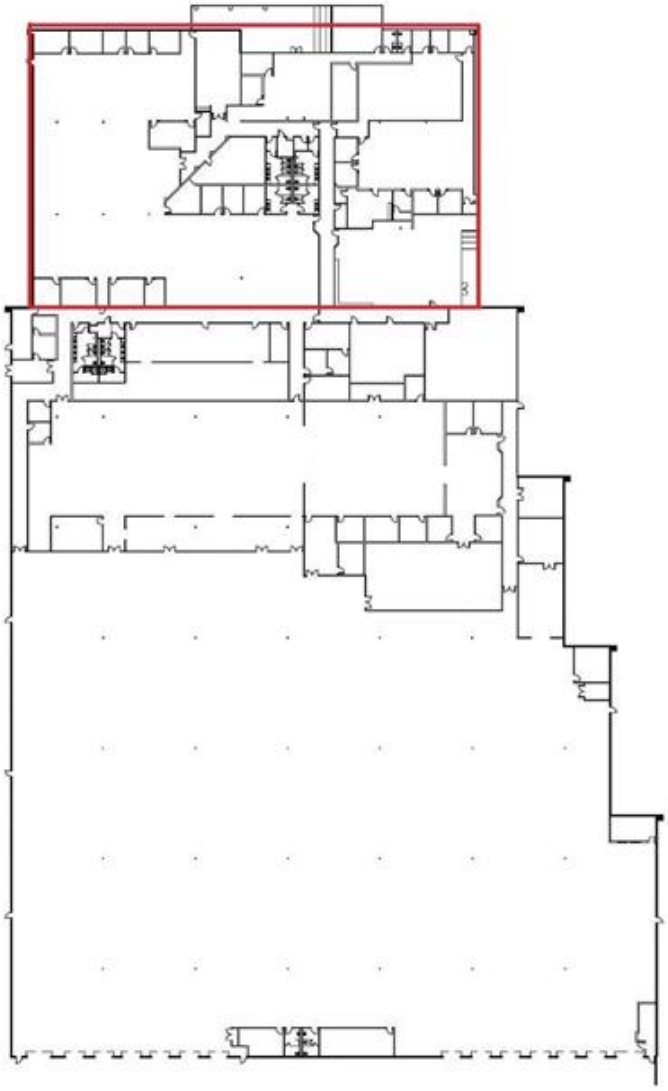
(e) If the two (2) appraisers fail to agree upon and appoint a third appraiser, either party, upon ten (10) days written notice to the other party, can apply to the Presiding Judge of the Superior Court of Los Angeles County to appoint a third appraiser meeting the qualifications set forth herein. The third appraiser, however, selected shall be a person who has not previously acted in any capacity for either party.

(f) The cost of each party's appraiser shall be the responsibility of the party selecting such appraiser, and the cost of the third appraiser (or arbitration, if necessary) shall be shared equally by Landlord and Tenant.

(g) If the process described hereinabove has not resulted in a selection of either Landlord's or Tenant's submitted best and final fair market rental rate by the commencement of the applicable Option Term, then the fair market rental rate estimated by Landlord will be used until the appraiser(s) reach a decision, with an appropriate rental credit and other adjustments for any overpayments of Monthly Base Rent or other amounts if the appraisers select Tenant's submitted best and final estimate of the fair market rental rate. The parties shall enter into an amendment to this Lease confirming the terms of the decision.

SCHEDULE 4.4.1

Landlord HVAC Installation Area (in Red)



[***]

SCHEDULE 13.1

Required Removables and Items Which May Be Left Behind

Required Removables:

[***]

Items Which May Be Left Behind:

[***]

Exhibit 4.13

Securities and Exchange Commission
100 F Street, NE
Washington DC 20549
USA

Our ref: SJM/63043/SMM

19 March 2019

Ladies & Gentlemen

We have read the statements made by Orchard Therapeutics PLC (copy attached), which we understand will be filed with the Securities and Exchange Commission, pursuant to Item 16 of Form 20-F of Orchard Therapeutics PLC on 22 March 2019. We agree with the statements concerning our firm contained therein.

Yours faithfully

Blick Rothenberg Audit LLP

Blick Rothenberg Audit LLP

Blick Rothenberg Audit LLP
16 Great Queen Street
Covent Garden
London WC2B 5AH

Tel: +44 (0)20 7486 0111
Fax: +44 (0)20 7935 6852
Email: email@blickrothenberg.com
Web: www.blickrothenberg.com

Exhibit 8.1

Subsidiaries

Name of Subsidiares	**Jurisdiction of Incorporation or Organization**
Orchard Therapeutics (Europe) Limited	England and Wales
Orchard Therapeutics North America	United States
Orchard Therapeutics (Netherlands) B.V.	Netherlands

Exhibit 12.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Mark Rothera, certify that:

1. I have reviewed this annual report on Form 20-F of Orchard Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the company as of, and for, the periods presented in this report;

4. The company's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the company and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

   (c) Evaluated the effectiveness of the company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the company's internal control over financial reporting; and

5. The company's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the company's auditors and the audit committee of the company's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the company's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the company's internal control over financial reporting.

Date: March 22, 2019

By: /s/ Mark Rothera

Mark Rothera
Chief Executive Officer
(Principal Executive Officer)

Exhibit 12.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Frank E. Thomas, certify that:

1. I have reviewed this annual report on Form 20-F of Orchard Therapeutics plc;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the company as of, and for, the periods presented in this report;

4. The company's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the company and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the company, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) (Paragraph omitted pursuant to SEC Release Nos. 33-8238/34-47986 and 33-8392/34-49313);

   (c) Evaluated the effectiveness of the company's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the company's internal control over financial reporting that occurred during the period covered by the annual report that has materially affected, or is reasonably likely to materially affect, the company's internal control over financial reporting; and

5. The company's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the company's auditors and the audit committee of the company's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the company's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the company's internal control over financial reporting.

Date: March 22, 2019

By: /s/ Frank E. Thomas

Frank E. Thomas
Chief Financial Officer

Exhibit 13.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

The certification set forth below is being submitted in connection with the Annual Report on Form 20-F for the year ended December 31, 2018 (the "Report") for the purpose of complying with Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code.

I, Mark Rothera, certify that:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 22, 2019

By: /s/ Mark Rothera
Mark Rothera
Chief Executive Officer

Exhibit 13.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

The certification set forth below is being submitted in connection with the Annual Report on Form 20-F for the year ended December 31, 2018 (the "Report") for the purpose of complying with Rule 13a-14(b) or Rule 15d-14(b) of the Securities Exchange Act of 1934 (the "Exchange Act") and Section 1350 of Chapter 63 of Title 18 of the United States Code.

I, Frank E. Thomas, certify that:

1. the Report fully complies with the requirements of Section 13(a) or 15(d) of the Exchange Act; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 22, 2019

By: /s/ Frank E. Thomas

Frank E. Thomas
Chief Financial Officer

Exhibit 15.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-228067) of Orchard Therapeutics plc of our report dated March 22, 2019 relating to the financial statements, which appears in this Form 20-F.

/s/ PricewaterhouseCoopers LLP
Reading, United Kingdom
March 22, 2019