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

FORM 10-K

(Mark One)

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

For the fiscal year ended December 31, 2022

OR

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

Commission File Number 001-38722

ORCHARD THERAPEUTICS PLC

(Exact name of Registrant as specified in its Charter)

England and Wales	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**

245 Hammersmith Road
London W6 8PW
United Kingdom
(Address of principal executive offices)

Registrant's telephone number, including area code: +44 (0) 203 808-8286

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
American Depositary Shares, each representing one ordinary share, nominal value £0.10 per share	ORTX	The Nasdaq Capital Market

Securities registered pursuant to Section 12(g) 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 ☒

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. 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, smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

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

If an emerging growth company, 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. ☐

Indicate by check mark whether the Registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ☐ NO ☒

As of the last business day of the Registrant's most recently completed second fiscal quarter, the aggregate market value of the Registrant's ordinary shares, nominal value £0.10 per share, held by non-affiliates was approximately $74 million, based on the last sale price of the Company's American Depositary Shares at the close of business on June 30, 2022.

As of March 10, 2023, the Registrant had 183,984,499 ordinary shares, nominal value £0.10 per share, outstanding, which if all held in ADS form would be represented by 18,398,449 American Depositary Shares, each representing ten ordinary shares.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement for its 2023 Annual General Meeting are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated.

Summary of the Material Risks Associated with Our Business

Our business is subject to numerous risks and uncertainties that you should be aware of in evaluating our business. These risks include, but are not limited to, the following:

- We have incurred net losses since inception. We expect to incur net losses for the foreseeable future and may never achieve or maintain profitability.
- We will need additional funding, which may not be available on acceptable terms or at all.
- 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.
- The results from our clinical trials for any of our product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the U.S. Food and Drug Administration or the European Medicines Agency may require us to conduct additional clinical trials or evaluate patients for an additional follow-up period.
- Interim data and ad hoc analyses are preliminary in nature. Success in pre-clinical studies or early clinical trials may not be indicative of results obtained in later trials.
- Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third-party manufacturers that are often our single source of supply.
- Libmeldy™, Strimvelis® and our product candidates and the process for administering Libmeldy, Strimvelis and our product candidates may cause serious or undesirable side effects or adverse events.
- 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.
- We may be unable to establish effective sales and marketing capabilities, which would negatively impact our revenue.
- If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy or any of our product candidates, if approved, our product revenues may be adversely affected.
- We face significant competition in our industry and there can be no assurance that our commercial products or our product candidates, if approved, will achieve acceptance in the market.
- We may experience disruptions in the development of our product candidates as the result of the COVID-19 pandemic.
- We may be unable to protect our intellectual property rights throughout the world.
- We may become subject to claims that we are infringing certain third-party patents.
- We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. These collaborations may not be successful.
- The market price of our ADSs may be highly volatile and may fluctuate due to factors beyond our control.

The summary risk factors described above should be read together with the text of the full risk factors below, in the section entitled “Risk Factors” in Part I, Item 1.A. and the other information set forth in this Annual Report on Form 10-K, including our consolidated financial statements and the related notes, as well as in other documents that we file with the U.S. Securities and Exchange Commission. The risks summarized above or described in full below are not the only risks that we face. Additional risks and uncertainties not precisely known to us, or that we currently deem to be immaterial may also materially adversely affect our business, financial condition, results of operations and future growth prospects.

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SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K, or 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 pre-clinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work and the period during which the results of the trials or studies will become available;
- the timing, scope and likelihood of regulatory submissions, filings and approvals, including our expectations and timing to prepare and submit a biologics license application, or BLA, for OTL-200 in mid-2023;
- our ability to develop and advance product candidates into, and successfully complete, clinical trials;
- our expectations regarding the market opportunity for and size of the patient populations for Libmeldy (OTL-200) and our product candidates, if approved for commercial use;
- the implementation of our business model and our strategic plans for our business, commercial products, product candidates and technology;
- our plans and ability to build out our commercial infrastructure and successfully identify eligible patients for Libmeldy in Europe and our product candidates, if approved for commercial use;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the pricing and reimbursement of Libmeldy and any of our product candidates, if approved, including reimbursement for patients treated in a country where they are not a resident;
- the adequacy, scalability and commercial viability of our manufacturing capacity, methods and processes, including those of our manufacturing partners, and our plans for future development;
- the rate and degree of market acceptance and clinical utility of our commercial products and product candidates and gene therapy in general;
- our ability to establish or maintain collaborations or strategic relationships or obtain additional funding;
- the impact of the COVID-19 global pandemic on our business operations;
- our competitive position;
- the scope of protection we and our licensors are able to establish and maintain for intellectual property rights covering our commercial products 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, clinical sites and manufacturers and their ability to perform adequately;

- our projected financial condition, including the sufficiency of our cash, cash equivalents and investments to fund operations in future periods and future liquidity, working capital and capital requirements; and
- other risks and uncertainties, including those listed under the caption “Item 1A. Risk Factors.”

You should refer to the section titled “Item 1A. 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. Business.

We are a global gene therapy company dedicated to transforming the lives of people affected by rare diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous hematopoietic stem cell, or HSC, gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. We seek to achieve this outcome by utilizing a lentiviral vector to introduce a functional copy of a missing or faulty gene into the patient's own, or autologous, HSCs through an *ex vivo* process, resulting in a gene-modified cellular drug product that can then be administered to the patient at the bedside.

To date, over 170 patients have been treated with our current and former product candidates across seven different diseases, with follow-up periods of more than 11 years following a single administration. We believe the data observed across these development programs, in combination with our expertise in the development, manufacturing and commercialization of gene and cell therapies, position us to provide potentially curative therapies to people suffering from a broad range of diseases.

We are currently focusing our *ex vivo* autologous HSC gene therapy approach on severe neurometabolic diseases and early research programs. Our lead program is OTL-200, which was approved in the European Union, the United Kingdom, Iceland, Liechtenstein and Norway under the brand name Libmeldy for eligible patients with early-onset metachromatic leukodystrophy, or MLD. Pending the outcome of the multidisciplinary pre-BLA meeting scheduled for the second quarter of 2023, we anticipate a potential BLA submission in mid-2023.

Our portfolio includes a commercial-stage product and research and development-stage product candidates. 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 and platelet lineage, thereby potentially enabling the correction of a wide range of diseases. By leveraging the innate self-renewing capability of HSCs that are engrafted in the bone marrow 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.

The diseases we target affect patients around the world, requiring an infrastructure to deliver gene therapies globally. In order to meet anticipated demand for our pipeline of approved products and product candidates still in development, we are utilizing our existing network of contract development and manufacturing organizations, or CDMOs, to manufacture lentiviral vectors and drug product. In addition, we have established process development capabilities in London, UK, and are leveraging technologies that will allow us to deliver our gene therapies globally.

Cryopreservation of our gene-modified HSCs is a key component of our commercialization strategy to deliver potentially curative gene therapies to patients worldwide, facilitating both local treatment and local or cross-border product reimbursement. We developed a cryopreserved formulation of Libmeldy (OTL-200) and are collecting supportive clinical data from patients treated with cryopreserved formulations to support the analytical comparability to the fresh cell formulations used in our registrational clinical trials. The registrational trials for all our earlier stage product candidates are expected to be conducted using a cryopreserved formulation.

With the exception of OTL-105, our product candidate for the potential treatment of hereditary angioedema, or HAE, which we are pursuing in partnership with Pharming Group N.V., we have global commercial rights to all our clinical product candidates and plan to commercialize our gene therapies in key markets worldwide, including in Europe and the U.S. initially, subject to obtaining the necessary marketing approvals for these jurisdictions. We are focused on deploying a commercial infrastructure to deliver Libmeldy and our product candidates, if approved, 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. In addition, we may rely on third parties to assist with regulatory submissions, disease awareness, patient identification and reimbursement in countries where local expertise is required or where we do not have a direct presence.

As we continue to develop our portfolio, we believe that the experience of our management team and our extensive academic relationships are key strategic strengths. Our management team has extensive experience in rare diseases and in the manufacturing, pre-clinical and clinical development and commercialization of gene and cell therapies. In addition, we partner with leading academic institutions around the world, which are pioneers in *ex vivo* autologous HSC-based 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 *ex vivo* autologous HSC gene therapy products.

Our *ex vivo* autologous HSC gene therapy approach

Our *ex vivo* autologous HSC gene therapy approach seeks to transform a patient's autologous HSCs into a gene-modified cellular 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, platelets and tissue resident macrophages, which include the microglia of the central nervous system. 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 mobilizing agents, which are agents that can move HSCs from the bone marrow into the peripheral blood for easier collection. The HSCs collected are then manufactured to insert a functional copy of the missing or faulty gene. 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 commercial and development programs. Since these cells are recognized by the body as the patient's own cells, the risks associated with using donor cells may be reduced. 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 broad range of different diseases.

Clinical validation already exists for hematopoietic stem cell transplantation, or HSCT, an approach of treating a patient with a genetic disease with HSCs contributed by a healthy donor individual, thereby using HSCs that contain a functioning copy of the gene of interest. However, this approach has significant limitations, including difficulties in finding appropriate genetically matched donors and the risk of graft-versus-host disease, transplant-related rejection and mortality from these and other complications, and is therefore typically only offered on a limited basis. Furthermore, genetically modified cells can be used to express enzyme activity at supra-physiological levels, which we believe has the potential to overcome the limitations of HSCT (where enzyme expression is generally limited to normal levels) to treat some neurometabolic disorders and improve the metabolic correction in neuronal cells before irreversible degeneration occurs. Our approach is intended to address these significant limitations of HSCT.

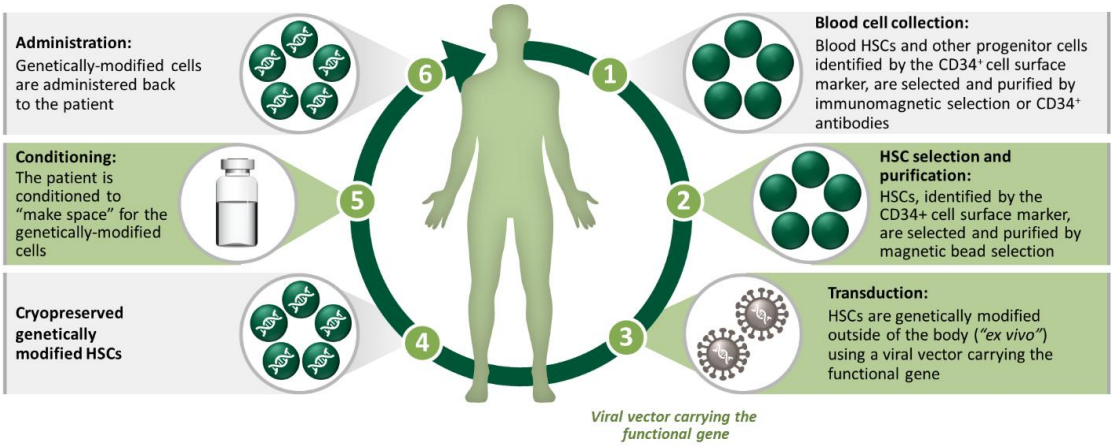
In a pre-clinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America,* or *PNAS*, a sub population of gene-modified HSCs has evidenced the potential to cross the blood-brain barrier, engraft in the brain as microglia and express genes and proteins within the central nervous system, one of the important physiological systems targeted by our HSC gene therapy approach. As published in *PNAS*, images taken during the study show a cross-section of the brain of a mouse that was infused intravenously with HSCs, which had been genetically modified using a lentiviral vector carrying green fluorescent protein, or GFP. The GFP expression observed throughout the brain illustrates the potential of gene-modified HSCs to cross the blood-brain barrier, engraft in the brain and express the functional protein throughout the brain, thereby potentially addressing a range of diseases that affect the central nervous system. Libmeldy (OTL-200), for instance, leverages this same mechanism of action to deliver gene-modified HSCs that can cross the blood-brain barrier and deliver a therapeutic gene that can prevent neuronal degeneration. The study demonstrated widespread distribution and expression of GFP in the brain of a mouse model following intravenous administration of HSCs transduced with GFP encoding vector.

With respect to Libmeldy (OTL-200) and each of our product candidates, our *ex vivo* gene therapy approach utilizes a self-inactivating, or SIN, 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 a cellular drug product that can then be re-introduced into the patient. Unlike some 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 functional gene into the HSCs and can lead to durable expression of the target protein by the gene-modified HSCs and their progeny after a single administration of gene therapy. In contrast, because AAV vectors rarely integrate into the genome, the transgene is not passed on to all progeny when the cell divides, resulting in rapid dilution and loss of the transgene among frequently dividing cells such as HSCs. Regarding immunogenicity, because *in vivo* delivery of AAV places the vector into direct contact with the immune system and most individuals harbor some type of pre-existing immunity, including neutralizing antibodies, to one or more types of AAV vector, the incoming vector can be completely inactivated by the patient's immune system. Furthermore, there have been reports that certain high dose applications of AAV have resulted in acute and severe innate immune responses that have proved lethal. With *ex vivo* delivery, however, the vector is not introduced directly into the body and

vector elements are washed away in the laboratory such that there is little to no vector element left to present to the immune system. Our HSC gene therapies and product candidates are all manufactured *ex vivo*.

Strimvelis for adenosine deaminase severe combined immunodeficiency, or ADA-SCID, is the only gammaretroviral vector-based gene therapy in our portfolio. In March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis.

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 market Libmeldy (OTL-200) and plan to market our current and any future product candidates, if approved, in a cryopreserved product formulation, which is designed to extend the drug product shelf life and enable the shipment of the drug product to specialized treatment centers, allowing patients to receive treatment closer to their home while leveraging more centralized manufacturing. Cryopreservation also allows us to conduct a number of quality control tests on the genetically 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 the number of patients that we may be able to treat, 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 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 third party commercial CDMOs with vector and drug product manufactured at such academic centers.

We are currently focused on employing our *ex vivo* autologous HSC gene therapy approach in two therapeutic disease areas: neurodegenerative and immunological disorders. We also have a program focused on beta thalassemia, or TDT, a blood disorder, but new investments in this program are currently limited. Data from clinical trials suggest that *ex vivo* autologous HSC gene therapy has the potential to provide generally well-tolerated, sustainable and improved outcomes over existing standards of care for diseases in these areas. We believe that we can apply our approach beyond our current target indications to treat an even broader range of diseases.

Our strategy

We are building a leading, global, fully-integrated gene therapy company focused on transforming the lives of people affected by severe diseases. To achieve this, we are pursuing the following strategies:

- Continue our commercialization efforts for Libmeldy (OTL-200) for treatment of eligible patients with early-onset MLD in Europe and expand geographically into new markets as regulatory approvals are obtained
- Advance our clinical-stage product candidates towards marketing approvals, including a potential BLA submission for OTL-200 in the U.S. in mid-2023

- Leverage the power of our therapeutic approach to investigate the potential of HSC gene therapy in larger indications
- Invest in new technologies and innovations to continue to improve our manufacturing processes for lentiviral vector and drug product and reduce costs of goods manufactured
- Establish end-to-end process development, manufacturing and supply chain capabilities, initially through third parties and internally over time
- Establish a patient-centric, global commercial infrastructure, including with third parties in certain regions where we do not have a direct presence
- Execute a business development strategy to leverage our HSC gene therapy approach, expand geographically, accelerate time-to-market or attract disease-area expertise to optimize the value of our portfolio of product candidates or expand into new indications

Our pipeline

Our pipeline spans multiple therapeutic areas where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

- Our programs focused on neurodegenerative disorders consist of our commercial program approved in Europe, Libmeldy (OTL-200) for MLD, two clinical proof of concept-stage programs, OTL-203 for MPS-I and OTL-201 for mucopolysaccharidosis type IIIA, or MPS-IIIA, and one pre-clinical program, OTL-204 for frontotemporal dementia with progranulin mutations, or GRN-FTD.
- Our programs in immunological disorders consist of two pre-clinical programs, OTL-104 for Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2, or NOD2-CD, and OTL-105 for HAE.
    - In July 2021, we entered into a collaboration with Pharming Group N.V., or Pharming, pursuant to which we granted Pharming worldwide rights to OTL-105. Under our agreement with Pharming, we will lead the completion of IND-enabling activities of OTL-105 and oversee its manufacturing during pre-clinical and clinical development, which will be funded by Pharming. Pharming will be responsible for clinical development, regulatory filings and commercialization of OTL-105, if approved, including associated costs.
    - We also have a commercial product approved in Europe, Strimvelis for ADA-SCID, an advanced registrational clinical program, OTL-103 for Wiskott Aldrich syndrome, or WAS, and one clinical proof of concept-stage program, OTL-102 for X-linked chronic granulomatous disease, or X-CGD. However, in March 2022, we announced that we would discontinue our investment in and seek alternatives for these programs.

The nature of our autologous gene therapy product candidates precludes the conduct of Phase 1 safety studies in healthy volunteers. Moreover, considering the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare indications with high unmet medical need, we believe our clinical programs will generally be eligible to proceed to registration based on a single pivotal study given the bioethical considerations regarding the conduct of randomized, double-blind and placebo-controlled clinical trials with gene therapies for such indications. 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.

Neurodegenerative Disorders

Gene therapy for treatment of MLD

Disease overview

MLD is a rare and life-threatening inherited disease of the body's metabolic system occurring in approximately one in every 100,000 live births in most regions of the world. Higher incidence rates are reported in geographies of higher consanguinity, such as Turkey and the Middle East. MLD is caused by a mutation in the arylsulfatase-A gene, or ARSA, that results in the accumulation of sulfatides in the brain and other areas of the body, including the liver, gallbladder, kidneys, and/or spleen. Over time, the nervous system is damaged, leading to neurological problems such as motor, behavioral and cognitive

regression, severe spasticity and seizures. Patients with MLD gradually lose the ability to move, talk, swallow, eat and see. In its late infantile form, mortality at five years from onset is estimated at 50% and 44% at 10 years for juvenile patients.

Limitations of current therapies

Prior to the approval of Libmeldy (OTL-200) in Europe, there were 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. MLD patients, their caregivers and families, and the healthcare system have faced significant burdens given the severity of the disease and the lack of effective treatments.

Our solution, Libmeldy (OTL-200) for treatment of MLD

OTL-200 is designed as a one-time therapy that aims to correct the underlying genetic cause of MLD, offering eligible patients the potential for long-term positive effects on cognitive development and maintenance of motor function at ages at which untreated patients show severe motor and cognitive impairments. With OTL-200, a patient's own HSCs are selected, and functional copies of the ARSA gene are inserted into the genome of the HSCs using a lentiviral vector before these genetically modified cells are infused back into the patient. The ability of the gene-corrected HSCs to migrate across the blood-brain barrier into the brain, engraft, and express the functional enzyme has the potential to persistently correct the underlying disease with a single treatment.

We obtained worldwide rights to this program through our asset purchase and license agreement with Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development LTD, or, together, GSK. The clinical trials for this program have been conducted under a GSK-sponsored clinical trial authorization, which was transferred to us during the third quarter of 2018.

Libmeldy approval in Europe as Orphan Drug

In December 2020, the European Commission granted full, or standard, marketing authorization for Libmeldy (OTL-200) (autologous CD34+ cell enriched population that contains hematopoietic stem and progenitor cells transduced *ex vivo* using a lentiviral vector encoding the human *arylsulfatase-A* (*ARSA*) gene) for the treatment of early-onset MLD characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.
Libmeldy has received orphan drug designation from the EMA for the treatment of MLD and orphan drug status was maintained at the time of approval. We are continuing to follow patients in the clinical development program for up to 15 years as a post-marketing commitment, and data will be presented to regulators at agreed time points in order to further characterize the long-term efficacy and safety of Libmeldy, particularly in the early symptomatic early juvenile population.

Data Supporting the Clinical Profile of Libmeldy

The European Commission (EC) approval is supported by clinical studies of Libmeldy in both pre- and early- symptomatic, early-onset MLD patients. Early-onset MLD encompasses the disease variants traditionally referred to as late infantile, or LI, and early juvenile, or EJ.

Clinical efficacy supporting EC approval was based on the integrated analysis of results from 29 patients with early-onset MLD who were all treated with Libmeldy:

- 20 patients were treated in a clinical study (median follow-up of 4 years); 9 patients were treated in expanded access programs (median follow-up of 1.5 years)
- 16 patients had a diagnosis of LI MLD; 13 had a diagnosis of EJ MLD
- At the time of treatment, 20 patients were deemed pre-symptomatic; 9 were deemed early-symptomatic

Clinical safety was evaluated in 35 patients with early-onset MLD:

- 29 patients from the efficacy analysis supporting EC approval (described above)
- 6 additional patients treated in another clinical study of Libmeldy

Co-primary endpoints

The co-primary endpoints of the integrated efficacy analysis were Gross Motor Function Measure, or GMFM, total score and ARSA activity, both evaluated at two years post-treatment. Results of this analysis indicate that a single-dose intravenous administration of Libmeldy is effective in modifying the disease course of early-onset MLD in most patients.
Pre-symptomatic LI and EJ patients treated with Libmeldy experienced significantly less deterioration in motor function at two years and three years post-treatment, as measured by GMFM total score, compared to age and disease subtype-matched untreated patients ($p \leq 0.008$). The mean difference between treated pre-symptomatic LI patients and age-matched untreated LI patients was 71.0% at year 2 and 79.8% at year 3. Similarly, the mean difference between treated pre-symptomatic EJ patients and age-matched untreated EJ patients was 52.4% at year 2 and 74.9% at year 3. Although not statistically significant, a clear difference in GMFM total score was also noted between treated early-symptomatic EJ patients and age-matched untreated EJ patients (28.7% at year 2; $p=0.350$ and 43.9% at year 3; $p=0.054$).

A statistically significant increase in ARSA activity in peripheral blood mononuclear cells was observed at 2 years post-treatment compared to pre-treatment in both pre-symptomatic patients (20.0-fold increase; $p<0.001$) and early-symptomatic patients (4.2-fold increase; $p=0.004$).

At the time of the integrated data analysis, all treated LI patients were alive with a follow-up post-treatment of up to 7.5 years and 10 out of 13 treated EJ patients were alive with a follow-up post-treatment of up to 6.5 years. No treatment-related mortality has been reported in patients treated with Libmeldy.

Key secondary endpoints

For EJ patients who were early-symptomatic when treated with Libmeldy, meaningful effects on motor development were demonstrated when these patients were treated before entering the rapidly progressive phase of the disease (IQ≥85 and Gross Motor Function Classification, or GMFC, ≤1). By 4 years post-disease onset, an estimated 62.5% of treated, early-symptomatic EJ MLD patients survived and maintained locomotion and ability to sit without support compared with 26.3% of untreated early-symptomatic EJ MLD patients, representing a delay in disease progression following treatment with Libmeldy.

A secondary efficacy endpoint that measured cognitive and language abilities as quantified by Intelligence Quotient/Development Quotient, or IQ/DQ, found in the treated LI subgroup, 12 out of 15 assessed patients had a fairly constant IQ/DQ, within the normal range (IQ/DQ score of 100 +/- SD of 15) throughout follow-up. All but two of these patients (i.e., one pre-symptomatic and one early-symptomatic) remained above the threshold of severe mental disability (IQ/DQ>55) at chronological ages at which all 14 untreated comparator LI patients showed evidence of severe cognitive impairment, which is defined as IQ/DQ below 55 and close to zero. Of the 10 surviving EJ patients, all 4 pre-symptomatic patients and 4 out of 6 early-symptomatic patients showed normal IQ/DQ throughout follow-up. In contrast, 11 out of 12 untreated EJ patients showed evidence of severe cognitive impairment during follow-up.

Clinical trial with cryopreserved drug formulation

The cryopreserved formulation of OTL-200 is being studied in a clinical trial of pediatric patients with pre-symptomatic LI, or pre- to early-symptomatic EJ in Milan, Italy.

The primary goal of this clinical trial is to assess the safety and efficacy of a cryopreserved formulation of OTL-200 in early-onset 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.

Ten patients were treated in this trial between April 2017 and April 2020. Data, which included six of these ten patients, was presented at WORLD Symposium in 2021. The median duration of follow up was 0.87 years as of November 2019. Administration was generally well tolerated in all patients, and for those with enough follow-up post-treatment, preliminary evidence of engraftment and restoration of ARSA activity in peripheral blood to supraphysiological levels and in cerebral spinal fluid, or CSF, to normal levels has been shown. The short-term safety profile was comparable between patients treated with the fresh formulation.

Data Supporting Safety Profile of Libmeldy

The safety of Libmeldy was evaluated in 35 patients with MLD.

The median duration of follow-up in the integrated safety data set, which included 29 patients treated with the fresh (investigational) formulation was 4.51 years. Three patients died and a total of 26 patients remained in the follow-up phase. The median duration of follow-up in the 6 patients treated with the cryopreserved (commercial) formulation was 0.87 years.

All treated LI patients were alive with a follow-up post-treatment of up to 7.5 years, and 10 out of 13 treated EJ patients were alive with a follow-up post-treatment of up to 6.5 years. No treatment-related mortality has been reported in patients treated with Libmeldy.

The most common adverse reaction attributed to Libmeldy was presence of anti-ARSA antibodies, or AAA. Five events of AAA were observed in four out of 35 patients and were related to treatment. Antibody titers were generally low and resolved either spontaneously or after a short course of rituximab. In all patients with positive AAA test results, no negative effects were observed in the post-treatment ARSA activity of peripheral blood or bone marrow cellular sub populations nor in the ARSA activity within the cerebrospinal fluid. No impact on the clinical efficacy or safety outcomes were observed.in any of the subjects who reported AAA. In addition to the risk associated with the gene therapy, treatment with Libmeldy is preceded by other medical interventions, namely bone marrow harvest or peripheral blood mobilization and apheresis, followed by myeloablative conditioning, which carry their own risks. During the clinical studies, the safety profiles of these interventions were consistent with their known safety and tolerability.

A total of 39 patients have been treated as part of the clinical development program between April 2010 and April 2020. An integrated data analysis comparing 39 treated patients to a natural history study cohort was presented at WORLD Symposium in 2023. Consistent with previously published results (Fumagalli et al Lancet 2022), these results combining the original 29 subjects with the 10 treated patients from the study evaluating the cryopreserved formulation, with longer follow-up (median 6.15 years, max 11.03 years), show a continued favorable benefit-risk profile for arsa-cel in pre-symptomatic LI and EJ and early-symptomatic EJ MLD. Arsa-cel was generally well tolerated with no treatment-related SAEs or treatment-related deaths.

For more details, please see the Summary of Product Characteristics, or SmPC, for Libmeldy.

OTL-200 development in the U.S.

OTL-200 has received orphan drug designation for the treatment of MLD as well as Rare Pediatric Disease designation. In late 2020, the FDA cleared our IND application for OTL-200 in the U.S., and in January 2021, FDA granted regenerative medicine advanced therapy, or RMAT, designation for OTL-200. Based on feedback received from the FDA, we are preparing for a BLA filing for OTL-200 in pre-symptomatic, early-onset MLD patients, expected in mid-2023, using data from existing OTL-200 patients. This approach and timeline are subject to the successful completion of activities remaining in advance of a pre-BLA meeting with the FDA, scheduled for the second quarter of 2023.

Gene therapy for treatment of MPS-IH

Disease overview

Mucopolysaccharidosis type I is a lysosomal storage disease caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase, or IDUA. Inherited deficiency of IDUA is responsible for MPS-I. Without treatment, clinical manifestations of this severe disease include skeletal abnormalities with severe orthopedic manifestations, hepatosplenomegaly, neurodevelopmental decline, sight and hearing disturbances, cardiovascular and respiratory problems leading to death in early childhood. IDUA deficiency can result in a wide range of clinical severity, with three major recognized clinical entities: (1) Hurler, or MPS-IH, (2) Scheie, or MPS-IS (3) and Hurler-Scheie, or MPS-IH/S, syndromes. MPS-IH is the most severe form of MPS-I.

The median age of diagnosis for MPS-IH is 12 months, and most affected children are diagnosed before 18 months of age. Infants affected by MPS-IH may appear normal at birth, but progress to develop symptoms such as kyphosis of the spine, and inguinal or umbilical hernias in the first six months, developing the characteristic somatic phenotype over the first few years of life.

The approximate incidence of MPS-I is of one in 100,000 live births. Approximately 60 percent of children born with MPS-I have MPS-IH.

Limitations of current therapies

Allogeneic-HSCT, or allo-HSCT, which is commonly accompanied by pre- and peri-transplant enzyme replacement therapy, or ERT, from diagnosis to engraftment, has been established as the standard of care for MPS-IH patients with preserved cognition. The recommendation of allo-HSCT as the standard of care for MPS-IH patients is endorsed by the European Society for Blood and Marrow Transplantation and the American Society for Transplantation and Cellular Therapy.

Despite its established position in treatment algorithms, allogeneic-HSCT can result in alloreactive complications, including and graft versus host disease or death, particularly when the degree of matching between graft donor and recipient is poor. Additionally, there remains a significant disease burden in those treated, even if treated early in life, including severely

debilitating cognitive, neurological, growth, orthopedic, cardiac, respiratory and ophthalmic manifestations, all of which are reported during long-term post-HSCT follow-up.

Our solution, OTL-203 for treatment of MPS-IH

Ex vivo autologous HSC gene therapy strategies aimed at correcting the genetic defect in patients could represent a significant improvement for the treatment of MPS-I, notably MPS-IH, the most severe and prevalent phenotype with the highest unmet medical need, when compared to current treatments.

OTL-203 is a single administration, gene therapy product candidate consisting of autologous CD34+ enriched HSPCs, derived from mobilized peripheral blood, genetically modified *ex vivo* with the lentiviral vector encoding for the IDUA complementary DNA, or cDNA. It is being developed as a cryopreserved formulation. *Ex vivo* autologous gene therapies, such as OTL-203, are designed to correct the genetic defect in patients' own HSCs and their progeny by addition of functional cDNA. The OTL-203 mechanism of action, or MOA, addresses the disease pathophysiology by restoring enzymatic IDUA expression in peripheral and central body compartments as well as restoring microglia homeostasis in the central nervous system, or CNS, to confer neuroprotective effects against the neurotoxic effects of glycosaminoglycan, or GAG, accumulation in affected cells.

The achievement of long-term sustained correction of the manifestations of MPS-IH occurs via local secretion of functional IDUA enzyme, which facilitates the efficient clearance of GAGs. This MoA is based on the local release of IDUA enzyme from genetically corrected cells containing functional copies of the *IDUA*gene into the extracellular space, which is in turn taken up by neighboring cells in a process referred to as "cross-correction." Animal models have shown that genetically modified cells are able to cross the blood brain barrier and can provide cross-correction within the CNS. Engraftment of these cells within the CNS gives rise to monocyte-derived microglia-like cells that secrete the functional IDUA enzyme, which is taken up by neuronal and glial cells via cross-correction.

One way in which OTL-203 differs from allo-HSCT is the ability of the transduced autologous cells to produce supraphysiological levels of IDUA enzyme in peripheral compartments and increased IDUA levels in central compartments in both non-clinical and clinical settings. This difference may be important because multivariate analyses have consistently identified higher post-HSCT IDUA levels as predictors of outcomes with lower residual disease burden in multiple organ systems, including skeletal, ophthalmic, cardiac, auditory and respiratory. It is therefore hypothesized that the presence of supraphysiological levels of IDUA enzyme in peripheral compartments may help overcome the limitations of allo-HSCT by enhancing the cross-correction process, by enabling presence of greater quantities of available enzyme in difficult-to-reach protected (i.e., brain) or avascular compartments (i.e., eye and joint tissue) and better enable clearance of GAGs in hard-to-reach tissues.

In addition, OTL-203 has the potential to overcome safety issues associated with the current standard of care. Compared to allogeneic transplantation, which is the current standard of care for MPS-IH treatment, the autologous nature of OTL-203 is associated with a significantly reduced transplant-related morbidity and mortality and avoidance of graft versus host (both acute and chronic) and immune mediated graft rejection.

We have obtained worldwide development and commercialization rights to OTL-203 from Telethon Foundation and San Raffaele Hospital.

OTL-203 has received orphan drug and PRIME designation from the EMA as well as orphan drug designation and rare pediatric disease designation from the FDA for the treatment of MPS-I.

Ongoing clinical trials

OTL-203 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 study is a prospective, single dose, single center, non-randomized, open label study involving a single administration of OTL-203 in eight patients with a confirmed diagnosis of MPS-IH. The study is fully enrolled using a cryopreserved formulation of OTL-203.

The patients evaluated in this trial include pediatric MPS-IH patients from 14 to 34 months of age at the time of treatment and will be followed for at least five years post-treatment in the context of the proof of concept study and then continue to be evaluated in a long-term follow-up study.

In September 2022, we announced the presentation of the interim clinical results from the ongoing academic-sponsored clinical trial at the San Raffaele Hospital. For this presentation's last follow up of all patients (range: 24 and 36 months), interim data supporting clinical proof-of-concept illustrated that treatment with OTL-203 was generally well-tolerated with a safety profile consistent with the selected conditioning regimen. IDUA antibodies present prior to gene therapy as a result of

ERT were not seen in any patient within three months following treatment. In addition, ERT was discontinued at least three weeks prior to any patient receiving gene therapy treatment, and no patients had re-started ERT post-treatment.

In December 2022 we received IND clearance of OTL-203 from the FDA, which allows us to initiate a global registrational study in MPS-IH. We plan to initiate the study, which will include centers across the US and Europe, in the second half of 2023.

The study will be a multi-center, randomized, active controlled clinical trial designed to evaluate the efficacy and safety of OTL-203 in patients with MPS-IH compared to standard of care with allogeneic hematopoietic stem cell transplant. A total of 40 patients with a confirmed diagnosis of MPS-IH who meet the study inclusion criteria will be randomized 1:1 to receive either OTL-203 or allogeneic HSCT. The study is powered to demonstrate superiority of OTL-203 over allo-HSCT.

Gene therapy for treatment of MPS-IIIA

Disease overviews

MPS-IIIA, also known as Sanfilippo syndrome type A, is a life-threatening metabolic disease that causes accumulation of glycosaminoglycan in cells, tissues and organs, particularly in the brain. Within the first years after birth, MPS-IIIA and MPS-IIIB patients begin to experience progressive neurodevelopmental delay and 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 is between 10 to 25 years.

The incidence of MPS-IIIA is currently estimated to be one in 100,000 live births per year.

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MPS-IIIA. 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 but does not slow or reverse the progression of the underlying disease. Systemic ERT is not an approved treatment option and HSCT is not considered to be an effective treatment option for these diseases. The severity of symptoms and lack of an effective treatment option to manage these symptoms is a significant burden to MPS-IIIA patients, their caregivers and families and healthcare systems.

Our solutions, OTL-201 for treatment of MPS-IIIA

We are developing OTL-201 as an *ex vivo* autologous HSC gene therapy for treatment of patients with MPS-IIIA. We believe pre-clinical studies in mice have shown that *ex vivo* autologous gene therapy has the potential to address the neurological manifestations of MPS-IIIA. We have obtained worldwide development and commercialization rights to OTL-201 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.

Proof of concept trial in MPS-IIIA

We are supporting a proof-of-concept trial for the treatment of MPS-IIIA, which started enrollment in January 2020. The trial, which is being conducted by the Royal Manchester Children's Hospital and sponsored by the Manchester University NHS Foundation Trust, completed enrollment in 2021 with the fifth patient treated in September 2021.

Early clinical findings, including the first neurocognitive results, from the proof-of-concept trial were presented at the American Society of Hematology (ASH) Annual Meeting in December 2022 and at the WORLD Symposium in February 2023. The data, which encompassed follow-up ranging from 9 to 24 months, showed robust, prompt, sustained, multi-lineage engraftment of genetically modified cells. Supraphysiological levels of SGSH enzyme were seen in leukocytes, plasma and CSF and rapid and reduction of substrate (glycosaminoglycans, GAGs) observed in all compartments.

Early neurocognitive outcomes also indicated that since receiving OTL-201, four out of five patients showed gain of cognitive skills in line with development in healthy children. The oldest patient at last follow up has maintained this normal cognitive development since treatment, despite reaching a chronological age where cognition is observed to decline in natural history patients, showing improvement from this comparator. Three additional patients are currently within the normal development quotient (DQ) range at 9 to 18 months post-treatment but require longer follow-up to assess outcomes.

Treatment with OTL-201 was generally well-tolerated in the initial study population. Of the six serious adverse events (SAEs) reported to date, four were determined to be due to conditioning or leukapheresis and one was related to background

disease. One patient had delayed platelet engraftment until day 52 post-treatment, likely due to Cytomegalovirus infection around the time of infusion.

Research program in FTD

Disease overview

Frontotemporal Dementia, or FTD, is the second most common cause of dementia after Alzheimer Disease in people under the age of 65. FTD is due to the atrophy of the frontal and temporal lobes of the brain. The disease manifests with progressive changes in behavior and personality, starting with symptoms such as decline in social and personal interactions, depression, apathy, emotional blunting, disinhibition and language disorders, and then progressing to general cognitive impairment at a later stage. In ~5% of patients, FTD is caused by mutations in one copy (haploinsufficiency) of the gene that codes for progranulin, or GRN. GRN is a neurotrophic, anti-inflammatory factor that is produced and secreted among others by specialized cells in the brain called microglia cells. GRN produced by microglia cells can be taken up by neighboring neurons, helping them to be healthy and functional. Since GRN-FTD patients' cells do not produce enough GRN, brain inflammation develops with time and neurons become progressively dysfunctional until they eventually die, leading to brain atrophy and the aforementioned symptoms.

We believe there are currently up to 2,500 people affected by GRN-FTD in Europe and the U.S., with approximately 800 new cases per year.

Limitations of current therapies

There are no treatments available for FTD and death occurs six to nine years after onset.

Our solution, OTL-204 for treatment of FTD

OTL-204 is an *ex vivo* autologous HSC gene therapy being developed to replace the defective microglia cells in the brain of GRN-FTD patients with genetically modified microglia cells that produce and secrete a corrective amount of GRN. These cells develop naturally from HSCs, which are collected from the patient and modified by using a viral vector that brings a functional copy of the GRN gene. When they are infused in the patient, the genetically modified HSCs naturally reach the brain and become resident microglia cells. OTL-204 is being developed in partnership with Professor Alessandra Biffi at the University of Padua in Italy. As part of the collaboration, we initiated a sponsored research agreement with the University of Padua and obtained an exclusive option with Boston Children's Hospital to develop and exclusively license the program.

Pre-clinical development of OTL-204

Preliminary *in vitro* data obtained in 2020 have demonstrated that human cell lines and mouse HSCs can be efficiently transduced to produce GRN. GRN is then secreted in the culture medium and can be taken up by other types of cells that do not produce GRN themselves.

Preliminary *in vivo* data from the pre-clinical proof-of-concept study showed that murine GRN-/- HSPCs, transduced with an LV expressing progranulin under the control of a novel promoter, are able to engraft and repopulate the brain myeloid compartment of FTD mice and to locally deliver the GRN enzyme.

Immunological Disorders

Research program in NOD2-Crohn's Disease

Disease overview

Crohn's Disease, or CD, is a form of Inflammatory Bowel Disease, or IBD, a condition affecting the gastrointestinal tract caused by an uncontrolled and chronic inflammatory process directed against intestinal bacteria. Mutations in a number of genes are known to confer susceptibility to the risk of CD, and among these the NOD2 gene (nucleotide-binding oligomerization domain-containing protein 2) is known to be the most common genetic factor, with 20-40% of Crohn's patients carrying mutations causing defective NOD2 activity. NOD2 encodes a cell receptor which controls bacterial elimination by innate immune cells such as macrophages through recognition of bacterial peptide (MDP) and induction of a pro-inflammatory immune response. NOD2 deficiency results in an impaired detection and clearance of bacteria penetrating the gut during gastrointestinal infection, creating an unchecked and relapsing inflammation within the intestinal tissues characterized by intestinal granuloma formation. This leads to recurrent clinical symptoms of chronic abdominal pain, diarrhea, weight loss, fatigue, malnutrition and for some patients, more severe intestinal damage requiring surgical resection. NOD2-CD patients typically present with more severe symptoms and are reported to be more refractory to existing therapies.

The incidence of CD is high compared to our other indications, with estimates of 100 to 200 patients per million in Europe and North America. Epidemiological studies suggest NOD2 genetic variants causing functional defects are associated with 7 to 10% of all cases of CD, with up to 200,000 patients in the U.S. and Europe with two NOD2 mutated alleles.

Limitations of current therapies

Current clinical management for Crohn's disease includes use of immune-suppressive medications, biological agents such as anti-TNF, steroids and surgical resection. There is currently no cure for Crohn's disease, and long-term, effective treatment options are limited. Several clinical trials have evaluated autologous HSCT in Crohn's disease, although with limited success. There remains a need for therapeutic modalities that target underlying causes of Crohn's disease to achieve effective amelioration of symptoms and disease remission.

Our solution, OTL-104 for treatment of NOD2-CD

We are developing OTL-104 to evaluate its therapeutic efficacy as an *ex vivo* autologous HSC gene therapy to treat patients with NOD2-CD through a single administration. As the pathogenesis of NOD2-CD is associated with the function of cells of the hematopoietic system, *ex vivo* autologous HSC gene therapy may therefore be used to restore NOD2 function to immune cells such as tissue resident macrophages within the gastrointestinal tract. Our OTL-104 program is being designed to introduce the NOD2 gene into cells of the hematopoietic system by lentiviral transduction of a patient's own blood or bone marrow derived HSCs, and the gene-modified cells can then be infused back into the patient. Clinical observations in the allogeneic transplant setting, where HSCT has resulted in the clinical reversion of Crohn's Disease and other monogenic forms of IBD, supports the scientific rationale and mode of action of OTL-104. We own patent applications in the United States and other jurisdictions and all other intellectual property rights associated with the OTL-104 program.

Pre-clinical development of OTL-104

OTL-104 pre-clinical work has shown that restoration of NOD2 gene expression in murine and human stem cells can rescue a defective myeloid immune response to MDP. NOD2 defective inflammatory functions in primary human myeloid cells can be restored by both lentiviral and gene editing approaches. The OTL-104 lentiviral vector is designed to express NOD2 under the chimeric CathepsinG/cFES promoter to deliver myeloid directed transgene expression. Pre-clinical studies to evaluate the safety of this approach show that NOD2-LV gene modification of human $CD34^+$stem cells and murine *lineage* negative stem cells does not affect HSC engraftment or immune subset development and differentiation following transplantation into NSG or NOD2-KO mice, respectively. Transplantation of NOD2-LV gene modified murine stem cells further demonstrates that HSC derived cells can efficiently migrate and reconstitute the myeloid cell compartments of intestinal tissue, restoring a normal biodistribution of NOD2 expression within the gut.

Pre-clinical proof-of-concept studies include *in vivo* colitis disease modeling and a non-interventional clinical research study using NOD2-genetically defined patients with Crohn's Disease. We have generated *in vivo* evidence that defective monocyte functions in NOD2-KO mice can be corrected by OTL-104 gene therapy, restoring NOD2-dependent systemic cytokine responses and innate immune cell mobilization. *In vitro*, myeloid cells differentiated from $CD34^+$ cells obtained from peripheral blood of genetically characterized NOD2 deficient CD patients, are refractory to MDP stimulation and unable to generate a normal cytokine response profile. LV transduction of NOD2-deficient patient cells restores MDP-induced cytokine responses to levels comparable to those observed in monocytes derived from $CD34^+$ cells from healthy donors, correcting a NOD2-defective phenotype. Orchard's OTL-104 program is currently under development towards IND-/ CTA- enabling toxicology / biodistribution studies.

Other programs

In March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 for treatment of WAS and OTL-102 for treatment of X-CGD.

Future applications of our* ex vivo *autologous HSC gene therapy approach

We believe that our versatile *ex vivo* autologous HSC gene therapy approach has the potential to deliver promising gene therapies to patients across a broad range of diseases. Although our near-term focus is on delivering our commercial and clinical-stage gene therapies to patients suffering from several rare diseases described above, we believe we can leverage our significant research and development experience and partnerships with academic institutions to identify other diseases in our target areas, including neurodegenerative, immunological and blood disorders, where *ex vivo* gene therapy may have a comparably higher probability of success as compared to other approaches our mid- to long-term strategy is to leverage our HSC gene therapy approach in additional larger indications, seeking development partnerships as the programs advance

towards the clinic. One partnership already established in 2021 is our collaboration with Pharming on OTL-105, as referenced above.

Our regulatory strategy

The nature of our autologous gene therapy product candidates precludes the conduct of Phase 1 safety studies in healthy volunteers. Moreover, considering the indications our product candidates are intended to treat, which are often fatal without treatment and which are rare indications with high unmet medical need, we believe our clinical programs will generally be eligible to proceed to registration based on a single pivotal study given the bioethical considerations regarding the conduct of randomized, double-blind and placebo-controlled clinical trials with gene therapies for such indications. Both the FDA and 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 judgment and these determinations may differ in the United States and the European Union.

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 the 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 the purposes of a regulatory submission but will be submitted to the applicable regulatory agencies for informational purposes. For the 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 or an expanded access 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 will make a determination as to whether the available data is sufficient to support a regulatory submission.

Manufacturing

The diseases we are targeting affect patients across the world. Therefore, we are implementing plans to enhance our partnerships with CDMOs and leverage technologies that will allow us to deliver our gene therapies globally.

Global supply network with experienced CDMOs

We currently partner with a network of experienced CDMOs, including AGC Biologics S.p.A. (formerly MolMed S.p.A.) and Oxford BioMedica, for the supply of our vectors and drug products, including Libmeldy. We have established relationships with commercial CDMO partners with the resources and capacity to meet our clinical and existing and expected initial commercial needs. Our CDMO partners also provide us with access to their state-of-the art manufacturing technologies.

Manufacturing efficiencies and scalability

We are investing in human capital and advancing manufacturing technologies for HSC-based autologous *ex vivo* gene therapies. We have licensed lentiviral vector stable cell line technologies from GSK, completed transduction enhancer screening processes, established a vector process development lab at a Catapult Network facility in the UK, and are in the process of building cell therapy and analytical development capabilities at our London, UK global headquarters. We seek to enhance our product and process understanding while actively exploring and developing innovative technologies for vector and drug product manufacturing to improve the efficiency and scalability of manufacturing processes with an ultimate goal to reliably manufacture high quality products for rare diseases and larger indications at lower cost. For example, we have identified and validated several transduction enhancing compounds in order to facilitate lentiviral vector entry into HSCs, showing a greater than 50% reduction in vector requirements. We continue to invest in our people to support the commercialization and life cycle management of our pipeline products.

Cryopreservation of our gene therapy programs

Cryopreservation of gene-modified cells is a key component of our strategy to deliver innovative, potentially curative gene therapies to patients worldwide. We have developed cryopreserved formulations of our OTL-200 program and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future

submissions for marketing approval in the United States and Europe. Our programs in OTL-203 and OTL-201 have already started or will start with cryopreserved formulations. 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 gene-modified 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 reduce the logistical burden on patients and their families.

Commercial operations

We have launched Libmeldy (OTL-200) for the treatment of early-onset MLD following receipt of full, or standard, marketing approval from the European Commission in December 2020. We have secured agreements with several major European markets, including the U.K., Italy, Germany and Sweden, to enable access and reimbursement for all eligible patients with MLD. In addition, we have secured the renewal of the early access program in France, under which the Company receives reimbursement for the treatment of any eligible patient with MLD. We have recognized revenue from commercial treatments from markets with reimbursement agreements, early access mechanisms, treatment abroad programs and European cross-border (S2) pathways. Subject to approval of OTL-200 by the FDA, we also plan to put in place commercial operations and treatment centers in the U.S.

We are building our commercial capabilities by employing individuals with broad experience in quality assurance and compliance, medical education, marketing, supply chain, sales, public policy, patient services, market access and product reimbursement. We will need to expand these capabilities as we continue to implement appropriate quality systems, compliance policies, systems and procedures, as well as internal systems and infrastructure in order to support our supply chain, qualify and train additional treatment centers, establish patient-focused programs, educate healthcare professionals, and secure reimbursement. The timing and conduct of these commercial activities will be dependent upon regulatory approvals and on agreements we have made or may make in the future with strategic collaborators.

As part of the commercialization process, we are engaged in discussions with stakeholders across the healthcare system, including public and private payors, patient advocates and organizations, and healthcare providers, to drive more timely patient identification through education, newborn screening, and diagnostic initiatives and to explore new payment models that we hope will enable broader patient access. We have initiated over a dozen newborn screening studies in Europe, the Middle East and the U.S., six of which are actively screening. To date, there have been three genetically confirmed cases of MLD after screening of approximately 96,000 newborns globally. One of these cases has been assessed clinically and referred for treatment with Libmeldy with the other two more recently identified patients pending clinical assessment.

We are engaging with European country- and regional-level payment authorities to negotiate further reimbursement and access for Libmeldy.

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, patents, know-how and trade secrets associated with each of our products and product candidates. However, we do not own any patents or patent applications that cover Libmeldy or any of our lead product candidates. We cannot guarantee that patents will issue from any of existing patent applications or from any patent applications that 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 our products and 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 Libmeldy, Strimvelis and each of our product candidates. Nonetheless, 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 will 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 OTL-200 and as discussed in detail in "—License agreements", we have exclusive, worldwide, sublicensable licenses pursuant to our asset purchase and license agreement with GSK, or the GSK Agreement, and the R&D Agreement to anonymized patient-level data arising from the clinical trials of OTL-200 and know-how, including other clinical data and production information relating to OTL-200.

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 to accommodate for administrative delays caused at the U.S. Patent and Trademark Office, or USPTO, or may be shortened if another patent has a terminal disclaimer 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 any additional issued U.S. patents 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, but 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, they may disagree with our assessment of the appropriate 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 its portfolio of approved and investigational rare disease gene therapies to us, which included Strimvelis and OTL-200 for MLD, among other programs. GSK also simultaneously novated to us their R&D Agreement with Telethon-OSR.

Under the GSK Agreement, we are subject to certain diligence obligations to develop and advance certain of the acquired product candidates. For example, we were required to 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. In December 2020, we received full, or standard, marketing authorization for Libmeldy in the European Union as well as the United Kingdom, Iceland, Liechtenstein and Norway.

We are also required to use commercially reasonable efforts to obtain a priority review voucher, or PRV, from the FDA for certain programs, including OTL-200, 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 certain programs. 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.

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. For example, for Libmeldy, we pay a tiered royalty rate at percentages from the mid-teens to the low twenties. 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 OTL-200 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 or commercialization activities of any of the programs under the GSK Agreement upon the occurrence of a serious adverse event, or SAE, if we believe such program poses a safety risk to patients and in certain additional situations. 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 our obligations to use best endeavors or commercially reasonable efforts, as applicable, 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 hypothetical license would only continue until such time as we cured our material breach, and we would be required to pay GSK all amounts we received 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 certain programs, including OTL-200 and Strimvelis.

Pursuant to the R&D Agreement, Telethon-OSR 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 certain other diseases, including MLD. At the time we entered into the novation agreement, GSK had completed development, launched and commercialized Strimvelis for ADA-SCID in the European Union, and had exercised its exclusive option to obtain exclusive licenses from Telethon-OSR to certain programs, including MLD. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID and MLD programs, among others, pursuant to the GSK Agreement and 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 European Union 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. 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 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, including OTL-200. 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.

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 on multiple occasions and most recently in April 2020.

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. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica. Additionally, we are obligated to pay low single-digit percentage 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.

Telethon-OSR license agreement

In May 2019, we entered into a license agreement with Telethon-OSR under which Telethon-OSR granted us an exclusive worldwide license for the research, development, manufacture and commercialization of *ex vivo* autologous HSC lentiviral based gene therapy products for the treatment of MPS-I, including MPS IH. Under the terms of the agreement, Telethon-OSR is entitled to receive an upfront payment, and we may be required to make milestone payments if certain development, regulatory and commercial milestones are achieved. Additionally, we will be required to pay Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

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 among our products and clinical programs:

- **MLD**: To our knowledge, beyond Libmeldy in Europe, there is currently no other effective treatment option for patients with MLD. HSCT, for example, has demonstrated limited efficacy in halting disease progression and is therefore not considered a standard of care for this disease. A number of alternative approaches to HSCT are under investigation. For instance, Homology Medicines is at the pre-clinical stage of developing an *in vivo* AAV gene therapy for MLD delivered intravenously, Passage Bio has a pre-clinical development program for MLD, and Affinia has a pre-clinical program for *in vivo* AAV gene therapy for MLD through lumbar puncture

(LP) administration. We are also aware that Takeda is investigating an ERT for MLD with a biweekly intrathecal infusion, and Denali Therapeutics is at the pre-clinical stage of developing a recombinant ARSA enzyme engineered to cross the blood-brain barrier.

- **MPS-I**: The current standard of care for MPS-IH patients is HSCT before the age of 30 months. We are aware that REGENXBIO is developing an AAV-based gene therapy, which is in Phase I trials and to be delivered intracisternally. bluebird bio and Immusoft have both reported that they are developing *ex vivo* cell therapies in the pre-clinical stage. For MPS-I patients that are not suitable candidates for HSCT because they lack a suitable donor, were diagnosed later in life, or have a less severe subtype of MPS-I, the current standard of care for the treatment of MPS-I involves regular intravenous injections of laronidase (Aldurazyme), an ERT commercialized by BioMarin and Sanofi Genzyme. A formulation of laronidase for intrathecal administration is currently under evaluation. JCR Pharmaceuticals is developing an ERT, which is in Phase I trials. Denali Therapeutics has an ERT program in the discovery stage.
- **MPS-IIIA**: There are currently no effective disease modifying treatment options for patients with MPS-IIIA. We are aware of three gene therapy candidates in clinical development. Lysogene is developing an AAV gene therapy product administered through intracerebral injections and regained global commercial rights after its collaboration with Sarepta Therapeutics terminated in July 2022; Abeona Therapeutics has been developing an AAV gene therapy product administered intravenously, which was licensed to Ultragenyx in May 2022 for further clinical development; and Esteve is developing an AAV gene therapy administered through intracerebroventricular injection. Amicus Therapeutics is at the pre-clinical stage of developing an AAV gene therapy for MPS-IIIA. JCR Pharmaceuticals and Denali Therapeutics each have a pre-clinical stage ERT program for MPS-IIIA.
- **GRN-FTD**: There are no approved disease modifying treatments for GRN-FTD. Each of Prevail Therapeutics (now owned by Eli Lilly & Company) and Passage Bio is developing in early-stage clinical trials an AAV gene therapy to be delivered intra-cisterna magna. Alector is developing a monoclonal antibody designed to increase levels of GRN in the brain in late-stage clinical trials, and Denali Therapeutics is developing a modified protein designed to penetrate across the blood-brain barrier at the pre-clinical stage in collaboration with Takeda.
- **NOD2-Crohn's**: There are no approved treatment options specifically for the NOD-2 form of Crohn's disease, and many patients with Crohn's disease have uncontrolled symptoms despite treatment with standard of care, including multiple anti-inflammatory biologics and surgical interventions. We are not aware of any other treatments in development specifically for the NOD-2 form of Crohn's disease.

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. 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.

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 good laboratory practices, or GLPs, unless justified, and applicable requirements for the humane use of laboratory animals or other applicable regulations;
- submission to the FDA of an application for an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an independent institutional review board, or 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 good clinical practices, or GCPs, and any additional requirements for the protection of human research subjects and their health information, to establish the safety and efficacy of the proposed biological product for its intended use;
- submission to the FDA of a biologics license application, or BLA, for marketing approval that includes sufficient evidence of establishing the safety, purity, and potency of the proposed biological product for its intended indication, including 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 current good manufacturing practice, or 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;
- review of the product candidate by an FDA advisory committee, where appropriate or if applicable;
- 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 pre-clinical testing stage. Pre-clinical 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 pre-clinical tests must comply with federal regulations and requirements including GLPs.

An IND is an exemption from the FD&C Act that allows an unapproved product candidate to be shipped in interstate commerce for use in an investigational clinical trial and a request for FDA authorization to administer such investigational product to humans. Such authorization must be secured prior to interstate shipment and administration of any product candidate that is not the subject of an approved BLA. In support of a request for an IND, applicants must submit a protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, the results of the pre-clinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, must be submitted to the FDA as part of an IND. The FDA requires a 30-day waiting period after the filing of each IND before clinical trials may begin. This waiting period is designed to allow the FDA to review the IND to determine whether human research subjects will be exposed to unreasonable health risks. At any time during this 30-day period the FDA may raise concerns or questions about the conduct of the trials as outlined in the IND and impose a clinical hold or partial clinical hold. In this case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can begin.

Following commencement of a clinical trial, the FDA may also place a clinical hold or partial clinical hold on that trial. A clinical hold is an order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. A partial clinical hold is a delay or suspension of only part of the clinical work requested under the IND. No more than 30 days after imposition of a clinical hold or partial clinical hold, the FDA will provide the sponsor a written explanation of the basis for the hold. Following issuance of a clinical hold or partial clinical hold, an investigation may only resume after the FDA has notified the sponsor that the investigation may proceed.

A sponsor may choose, but is not required, to conduct a foreign clinical trial under an IND. When a foreign clinical trial is conducted under an IND, all FDA IND requirements must be met unless waived. When a foreign clinical trial is not conducted under an IND, the sponsor must ensure that the study complies with certain regulatory requirements of the FDA in order to use the study as support for an IND or application for marketing approval or licensing. In particular, such studies must be conducted in accordance with GCP, including review and approval by an independent ethics committee, or IEC, and informed consent from subjects. The FDA must be able to validate the data through an onsite inspection, if deemed necessary by the FDA.

An IRB representing each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must conduct continuing review and re-approve the study at least annually. The IRB must review and approve, among other things, the study protocol and informed consent information to be provided to study subjects. An IRB must operate in compliance with FDA regulations. An IRB can suspend or terminate approval of a clinical trial at its institution, or an institution it represents, if the clinical trial is not being conducted in accordance with the IRB's requirements or if the product candidate has been associated with unexpected serious harm to patients.

Some trials are overseen by an independent group of qualified experts organized by the trial sponsor, known as a data safety monitoring board or committee, or DSMB. This group provides authorization as to whether or not a trial may move forward at designated check points based on access that only the group maintains to available data from the study.

In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules are subject to oversight of institutional biosafety committees, or IBCs, as set forth in the NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, or NIH Guidelines. Under the NIH Guidelines, recombinant and synthetic nucleic acids are defined as: (i) molecules that are constructed by joining nucleic acid molecules and that can replicate in a living cell (i.e., recombinant nucleic acids); (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules (i.e., synthetic nucleic acids); or (iii) molecules that result from the replication of those described in (i) or (ii). Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

Information about clinical trials must be submitted within specific time frames to the NIH for public dissemination on its ClinicalTrials.gov website.

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 generally recommends that sponsors of human gene therapy products integrating vectors such as gammaretroviral and lentiviral vectors and transposon elements 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 judgment 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, 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.

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, for example, by three months if the BLA sponsor submits a major new clinical study report, a major re-analysis of a previously submitted study or other major amendment at any time during the review cycle.

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, pure and potent, for its intended use, and whether the product is being manufactured in accordance with cGMP to ensure the continued safety, purity and potency of such product. 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 Risk Evaluation and Mitigation Strategy, or REMS, 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. During the COVID-19 pandemic, restrictions preventing the conduct or completion of facility or clinical site inspections have led to FDA deferred action on marketing applications or the issuance of complete response letters. 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 for the same use or indication, and we are unable to demonstrate that our product is clinically superior to the previously approved drug for the same use or indication. 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.

Rare Pediatric Disease Designation and Priority Review Vouchers

Under the FD&C Act, the FDA incentivizes the development of drugs and biological products that meet the definition of a "rare pediatric disease," defined to mean 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 United States or affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making in the United States a drug or biological product for such disease or condition will be received from sales in the United States of such drug or biological product. The sponsor of a product candidate for a rare pediatric disease may be eligible for a voucher that can be used to obtain a priority review for a subsequent human drug or biological product application after the date of approval of the rare pediatric disease drug or biological product, referred to as a priority review voucher, or PRV. A sponsor may request rare pediatric disease designation from the FDA prior to the submission of its BLA. A rare pediatric disease designation does not guarantee that a sponsor will receive a PRV upon approval of its BLA. Moreover, a sponsor who chooses not to submit a rare pediatric disease designation request may nonetheless receive a PRV upon approval of their marketing application if they request such a voucher in their original marketing application and meet all of the eligibility criteria. If a PRV is received, it may be sold or transferred an unlimited number of times. Congress has extended the PRV program through September 30, 2024, with the potential for PRVs to be granted through September 30, 2026.

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. Under the Food and Drug Omnibus Reform Act of 2022, or FDORA, the FDA is permitted to require, as appropriate, that a post-approval confirmatory study or studies be underway prior to approval or within a specified time period after the date of accelerated approval was granted. FDORA also requires sponsors to send updates to the FDA every 180 days on the status of such studies, including progress toward enrollment targets, and the FDA must promptly post this information publicly. FDORA also gives the FDA increased authority to withdraw approval of a drug or biologic granted accelerated approval on an expedited basis if the sponsor fails to conduct such studies in a timely manner, send the necessary updates to the FDA, or if such post-approval studies fail to verify the drug's predicted clinical benefit. Under FDORA, the FDA is empowered to take action, such as issuing fines, against companies that fail to conduct with due diligence any post-approval confirmatory study or submit timely reports to the agency on their progress. In addition, for products being considered for accelerated approval, the FDA generally requires, unless otherwise informed by the agency, that all advertising and promotional materials intended for dissemination or publication within 120 days of marketing approval be submitted to the agency for review during the pre-approval review period.

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 and those supplying products, ingredients and components of them, 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 USPTO, 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. This six-month exclusivity, which runs from the end of other exclusivity protection, 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.

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.

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. 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.

Clinical trials regulation

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 April 2014, the EU adopted the new Clinical Trials Regulation (EU) No 536/2014, or Regulation, which replaced the Clinical Trials Directive 2001/20/EC, or Directive, on January 31, 2022. The transitory provisions of the new Regulation provide that, by January 31, 2025, all ongoing clinical trials must have transitioned to the new Regulation. The new Regulation overhauled the system of approvals for clinical trials in the EU. Specifically, the new Regulation, which is directly applicable in all Member States (meaning that no national implementing legislation in each EU Member State is required), aims at simplifying and streamlining the approval of clinical trials in the EU. The main characteristics of the regulation include: a streamlined application procedure via a single-entry point through the Clinical Trials Information System, or CTIS; a single set of documents to be prepared and submitted for the application as well as simplified reporting procedures for clinical trial sponsors; and a harmonized procedure for the assessment of applications for clinical trials, which is divided in two parts (Part I contains scientific and medicinal product documentation and Part II contains the national and patient-level documentation). Part I is assessed by a coordinated review by the competent authorities of all EU Member States in which an application for authorization of a clinical trial has been submitted (Member States concerned) of a draft report prepared by a Reference Member State. Part II is assessed separately by each Member State concerned. Strict deadlines have been established for the assessment of clinical trial applications. The role of the relevant ethics committees in the assessment procedure will continue to be governed by the national law of the concerned EU Member State. However, overall related timelines will be defined by the Clinical Trials Regulation.

Drug review and approval

In the EU, medicinal products, including advanced therapy medicinal products, or ATMPs, are subject to extensive pre- and post-market regulation by regulatory authorities at both the EU and national levels. ATMPs comprise gene therapy products, somatic cell therapy products and tissue engineered products. Gene therapy products deliver genes into the body that lead to a therapeutic, prophylactic or diagnostic effect. Libmeldy is authorized as a gene therapy product in the EU, and we anticipate that our gene therapy development products would also be regulated as ATMPs in the EU.

To obtain regulatory approval of an ATMP under EU regulatory systems, we must submit an MAA under the centralized procedure administered by the EMA. The application used to submit the BLA in the United States is similar to that required in the EU, with the exception of, among other things, certain specific requirements set out in Regulation (EC) No 1394/2007 on advanced therapy medicinal products, or the ATMP Regulation, for example certain particulars to be contained in the summary of product characteristics. The centralized procedure provides for the grant of a single marketing authorization by the European Commission that is valid across all of the EU, and in the additional Member States of the European Economic Area (Iceland, Liechtenstein and Norway), or EEA. As provided for in the ATMP Regulation, the scientific evaluation of MAAs for ATMPs is primarily performed by a specialized scientific committee called the Committee for Advanced Therapies, or CAT. The CAT prepares a draft opinion on the quality, safety and efficacy of the ATMP which is the subject of the MAA, which is sent for final approval to the Committee for Medicinal Products for Human Use, or CHMP. The CHMP recommendation is then sent to the European Commission, which adopts a decision binding in all EU Member States. The maximum time frame for the evaluation of an MAA for an ATMP is 210 days from receipt of a valid MAA, excluding clock stops when additional information or written or oral explanation is to be provided by the applicant in response to questions asked by the CAT and/or CHMP. Clock stops may extend the time frame of evaluation of an MAA considerably beyond 210 days. Where the CHMP gives a positive opinion, the EMA provides the opinion together with supporting documentation to the European Commission, who make the final decision to grant a marketing authorization, which is issued within 67 days of receipt of the EMA's recommendation. Accelerated assessment may be granted by the CHMP in exceptional cases, when a medicinal product is of major public health interest, particularly from the viewpoint of therapeutic innovation. If the CHMP accepts such a request, the time frame of 210 days for assessment will be reduced to 150 days (excluding clock stops), but it is possible that the CHMP may revert to the standard time limit for the centralized procedure if it determines that the application is no longer appropriate to conduct an accelerated assessment.

Now that the UK (which comprises Great Britain and Northern Ireland) has left the EU, Great Britain is no longer covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations continue to be recognized in Northern Ireland). All medicinal products with an existing centralized marketing authorization were automatically converted to Great Britain marketing authorizations on January 1, 2021. For a period of three years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, could rely on a decision taken by the European Commission on the approval of a new marketing authorization in the centralized procedure, in order to more quickly grant a new Great Britain marketing authorization. A separate application will, however, still be required. On January 24, 2023, the MHRA announced that a new international recognition framework will be put in

place from January 1, 2024, which will have regard to decisions on the approval of marketing authorizations made by the European Medicines Agency and certain other regulators when determining an application for a new Great Britain marketing authorization.

Data and marketing exclusivity

The EU also provides opportunities for market exclusivity. Upon receiving a marketing authorization in the EU, innovative medicinal products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents generic or biosimilar applicants from referencing the innovator's pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar marketing authorization during a period of eight years from the date on which the reference product was first authorized in the EU. 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 period. The overall ten-year period will be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to authorization, is held to bring a significant clinical benefit in comparison with existing therapies. Even if an innovative medicinal product gains the prescribed period of data exclusivity, another company may market another version of the product if such company obtained marketing authorization based on an MAA with a complete and independent data package of pharmaceutical tests, pre-clinical tests and clinical trials. There is, however, no guarantee that a product will be considered by the EU's regulatory authorities to be an innovative medicinal product, and products may therefore not qualify for data exclusivity.

Orphan designation and exclusivity

Products with an orphan designation in the EU can receive ten years of market exclusivity, during which time "no similar medicinal product" for the same indication may be placed on the market. A "similar medicinal product" is defined as a medicinal product containing a similar active substance or substances as contained in an authorized orphan medicinal product, and which is intended for the same therapeutic indication. An orphan medicinal product can also obtain an additional two years of market exclusivity in the EU where an agreed pediatric investigation plan for pediatric studies has been complied with. 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 EU 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 an orphan medicinal product if it meets the following criteria: (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; and (2) either (i) the prevalence of such condition must not be more than five in 10,000 persons in the EU when the application is made, or (ii) without the benefits derived from orphan status, it must be unlikely that the marketing of the medicine would generate sufficient return in the EU to justify the investment needed for its development; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the EU, 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 designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the MAA if the orphan designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. A marketing authorization may be granted to a "similar medicinal product" for the same orphan indication at any time if:

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

Since January 1, 2021, a separate process for orphan designation has applied in Great Britain. There is now no pre-marketing authorization orphan designation (as there is in the EU) in Great Britain and the application for orphan designation will be reviewed by the MHRA at the time of an MAA for a UK or Great Britain marketing authorization. The criteria for orphan designation are the same as in the EU, save that they apply to Great Britain only (e.g., there must be no satisfactory method

of diagnosis, prevention or treatment of the condition concerned in Great Britain, as opposed to the EU, and the prevalence of the condition must not be more than five in 10,000 persons in Great Britain).

Pediatric development

In the EU, companies developing a new medicinal product must agree upon a pediatric investigation plan, or PIP, with the EMA's Pediatric Committee, or PDCO, 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 PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the product for which a marketing authorization is being sought. The MAA 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 by the PDCO of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults, in which case the pediatric clinical trials must be completed at a later date. Products that are granted a marketing authorization with the results 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, or SPC (provided an application for such extension is made at the same time as filing the SPC application for the product, or at any point up to 2 years before the SPC expires) even where the trial results are negative. In the case of orphan medicinal products, a two-year extension of the orphan market exclusivity may be available. This pediatric reward is subject to specific conditions and is not automatically available when data in compliance with the PIP are developed and submitted.

PRIME Designation

In March 2016, the EMA launched an initiative to facilitate development of product candidates in indications, often rare, for which few or no therapies currently exist. The PRIority MEdicines, or PRIME, scheme is intended to encourage drug development in areas of unmet medical need and provides accelerated assessment of products representing substantial innovation, where the MAA will be made through the centralized procedure. Eligible products must target conditions for which there is an unmet medical need (there is no satisfactory method of diagnosis, prevention or treatment in the EU or, if there is, the new medicine will bring a major therapeutic advantage) and they must demonstrate the potential to address the unmet medical need by introducing new methods of therapy or improving existing ones. Products from small- and medium-sized enterprises may qualify for earlier entry into the PRIME scheme than larger companies. Many benefits accrue to sponsors of product candidates with PRIME designation, including but not limited to, early and proactive regulatory dialogue with the EMA, frequent discussions on clinical trial designs and other development program elements, and accelerated MAA assessment once a dossier has been submitted. Importantly, a dedicated EMA contact and rapporteur from the CHMP or CAT are appointed early in the PRIME scheme facilitating increased understanding of the product at the EMA's Committee level. A kick-off meeting initiates these relationships and includes a team of multidisciplinary experts at the EMA to provide guidance on the overall development and regulatory strategies. Where, during the course of development, a medicine no longer meets the eligibility criteria, support under the PRIME scheme may be withdrawn.

Post-approval controls

Following approval, the holder of the marketing authorization is required to comply with a range of requirements applicable to the manufacturing, marketing, promotion and sale of the medicinal product. These include the following:

- 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 EU. Although general requirements for advertising and promotion of medicinal products are established under EU directives, the details are governed by regulations in each EU Member State and can differ from one country to another.

The aforementioned EU rules are generally applicable in the EEA.

Brexit and the Regulatory Framework in the UK

The UK left the EU (commonly referred to as "Brexit") in January 2020. The UK and EU entered a trade and cooperation agreement, or TCA, which has been formally applicable since May 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not provide for wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework continues to apply in Northern Ireland). Except in respect of the new EU Clinical Trials Regulation, the regulatory regime in Great Britain therefore largely aligns with current EU regulations. However, it is possible that these regimes will diverge more significantly in future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. However, notwithstanding that there is no wholesale recognition of EU pharmaceutical legislation under the TCA, under the new framework mentioned above which will be put in place by the MHRA from January 1, 2024, the MHRA has stated that it will take into account decisions on the approval of marketing authorizations from the EMA (and certain other regulators) when considering an application for a Great Britain marketing authorization.

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 federal Health Insurance Portability and Accountability Act of 1996, 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 "whistle blower" 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 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 federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, 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. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners;
- 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 payor. 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 (e.g., the California Consumer Privacy Act), many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

We may also be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the European Economic Area, or EEA, including personal health data, is subject to the General Data Protection Regulation 2016/679 (EU GDPR), which became effective in May 2018. Following Brexit and the expiration of the subsequent transition period on December 31, 2020, the EU GDPR has been brought into UK law as the "UK GDPR" which, along with the UK Data Protection Act 2018, governs the collection, use, storage, disclosure, transfer, or other processing of personal data regarding individuals in the UK. In the present document, references to "GDPR" are meant to include both the EU GDPR and the UK GDPR, unless specified. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data.

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 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 programs for Strimvelis and Libmeldy were approved by the EMA in 2016 and 2020, respectively, and the approval and commercialization of Strimvelis and Libmeldy 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

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes that affect the healthcare system and which could prevent or delay marketing approval of our potential products, restrict or regulate post-approval activities and affect our ability to profitably sell products, if approved.

In the United States, there have been and continue to be a number of legislative initiatives to contain healthcare costs. As one example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the ACA, was passed, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacted the U.S. pharmaceutical industry. Since its enactment, there have been numerous judicial, administrative, executive and legislative challenges to certain aspects of the ACA, as we expect there will be additional challenges and amendments to the ACA in the future.

In Europe, delivery of healthcare is largely a matter of national law and policy. National governments and health service providers have different priorities and approaches to the delivery of health care and the pricing and reimbursement of products in that context. Budgetary constraints could affect our ability to profitably sell approved products in certain jurisdictions.

We expect that healthcare reform measures may result in more rigorous coverage criteria and downward pressure on the price that we receive for approved products. There have been, and likely will continue to be, legislative and regulatory proposals at the foreign, federal and state levels directed at lowering the cost of healthcare. The implementation of cost containment measures or other healthcare reforms may prevent us from generating sufficient revenue, attaining profitability or commercializing additional products.

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. Patients who are prescribed treatments for their conditions and providers generally rely on these third-party payors to reimburse all or part of the associated healthcare. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor 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 and manufacturing costs.

The Inflation Reduction Act of 2022, or IRA, includes several provisions that may impact our business to varying degrees, including provisions that reduce the out-of-pocket cap for Medicare Part D beneficiaries to $2,000 starting in 2025; impose new manufacturer financial liability on certain drugs under Medicare Part D, allow the U.S. government to negotiate Medicare Part B and Part D price caps for certain high-cost drugs and biologics without generic or biosimilar competition, require companies to pay rebates to Medicare for certain drug prices that increase faster than inflation, and delay the rebate rule that would limit the fees that pharmacy benefit managers can charge. Further, under the IRA, orphan drugs are exempted from the Medicare drug price negotiation program, but only if they have one rare disease designation and for which the only approved indication is for that disease or condition. If a product receives multiple rare disease designations or has multiple approved indications, it may not qualify for the orphan drug exemption. The effects of the IRA on our business and the healthcare industry in general is not yet known.

In addition, coverage and reimbursement for products can differ significantly from payor to payor. One payor's decision to cover a particular medical product or service does not ensure that other payors will also provide coverage for the medical product or service, or will provide coverage at an adequate reimbursement rate. 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. CMS decides whether and to what extent a new medicine will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree.

Additionally, the coverage determination process will require us to provide scientific and clinical support for the use of our products to each payor 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 evidence generation studies in order to demonstrate the medical necessity and cost-effectiveness of such a product, in addition to the costs required to obtain regulatory approvals. If payors do not consider a product to be cost-effective compared to current standards of care, 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 cover its costs or make a profit.

Outside of the United States, the pricing of pharmaceutical products is subject to governmental control in many countries. For example, in the EU, 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 with the government authority. Furthermore, some countries may require the completion of additional studies that compare the effectiveness and/or cost-effectiveness of a particular therapy to current standards of care as part of so-called health technology assessments, or HTAs, in order to obtain reimbursement or pricing approval. Additionally, there may be a need for activities to secure reimbursement for procedures associated with products administered in a hospital setting, such as Libmeldy, under the diagnosis-related group, or DRG, system, whereby a billing code may not exist or may be currently insufficient to cover the cost of the procedure. In other instances, countries may monitor and control product volumes and issue guidance to physicians to limit prescriptions in the form of treatment policies. Efforts to control prices and utilization of pharmaceutical products will likely continue as countries attempt to manage healthcare expenditures.

Employees and Human Capital Resources

As of December 31, 2022, we had 166 full-time employees. 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 positive. We monitor employee engagement through an annual survey and develop a prioritized action plan on an annual basis to address any areas in need of attention. Our human capital objectives include, as applicable, identifying, recruiting, developing, retaining, and incentivizing our existing and prospective employees, as well as optimizing the overall employee experience. The principal purposes of our incentive plans are to attract, retain and motivate our employees. The granting of share-based compensation awards is designed to reward selected employees for long-term shareholder value creation and our cash-based performance bonus awards reward the achievement of annual performance goals. The health and safety of our employees, customers and communities are of primary concern. During the COVID-19 pandemic, we have taken significant steps to protect our workforce, including, but not limited to, implementing a hybrid work model and social distancing protocols consistent with guidelines issued by federal, state and local laws.

Corporate Information

We were originally incorporated under the laws of England and Wales in August 2018 as Orchard Rx Limited (now known as Orchard Therapeutics plc) to become a holding company for Orchard Therapeutics (Europe) Limited (previously known as Orchard Therapeutics Limited). Orchard Rx Limited subsequently re-registered as a public limited company and its name was changed from Orchard Rx Limited to Orchard Therapeutics plc in October 2018. Orchard Therapeutics (Europe) 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 and to Orchard Therapeutics (Europe) Limited in October 2018. Our registered office is located at 245 Hammersmith Road, London W6 8PW, United Kingdom, and our telephone number is +44 (0) 203 808 8286. 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 you should not consider any information on, or that can be accessed through, our website as part of this Annual Report. We make available free of charge through our website our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file or furnish such materials to the U.S. Securities and Exchange Commission.

Item 1A. 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 prospects. This Annual Report also contains forward-looking statements that involve risks and uncertainties. Our results could materially differ from those anticipated in 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 "Special Note 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 $150.7 million and $144.6 million for the twelve months ended December 31, 2022 and 2021, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares, through sales of our ADSs in our initial public offering and follow-on offering, and through private placements of our ordinary shares. We have devoted substantially all of our efforts to research and development, including clinical and pre-clinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Libmeldy in the European Union, building a global commercial infrastructure to support commercialization of Libmeldy (OTL-200) and our product candidates if such product candidates are approved, as well as to building our team. Absent the realization of sufficient revenue from product sales of Libmeldy and from sales of our current or future product candidates, if approved, we may never attain profitability.

We expect to continue to incur significant expenses and operating losses for the foreseeable future, particularly if, and as, we:

- seek marketing approvals for our product candidates that successfully complete clinical trials or meet primary endpoints, if any;
- market and sell Libmeldy in Europe and grow our commercial infrastructure for the commercialization (or anticipated commercialization) of any product candidates that we may submit for and obtain marketing approval anywhere in the world;
- continue the development of our product candidates;
- continue our ongoing clinical trials and any required regulatory updates for certain de-prioritized programs;
- conduct investigational new drug application, or IND, or clinical trial application, or CTA, enabling studies for our pre-clinical programs;
- initiate additional clinical trials and pre-clinical studies for our other product candidates or future product candidates, including new research programs in genetic subsets of frontotemporal dementia, or FTD, and Crohn's disease;
- 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, to support technology and process innovation, and to support manufacturing of product to commercial scale;
- establish partnerships with contract development and manufacturing organizations, or CDMOs;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility in the long-term;
- hire and retain personnel, such as non-clinical, clinical, pharmacovigilance, quality, regulatory affairs, process development and control, manufacturing, supply chain, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- encounter delays or setbacks in the pre-clinical testing, enrollment or conduct of our clinical trials for our product candidates, encounter delays in regulatory review timelines, or experience high levels of absenteeism due to the COVID-19 pandemic;
- develop, maintain, expand and protect our intellectual property portfolio; and

- comply with our obligations as a public company.

Since receiving marketing authorization, only a limited number of patients have been treated with Libmeldy. There is no assurance that revenue from sales of Libmeldy alone will be sufficient for us to become profitable. 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 as we seek to complete necessary pre-clinical studies and clinical trials of our product candidates, and manufacture, market and sell Libmeldy 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 revenue that is 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 limited sales revenue to date, 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 generated revenue from the sale of Libmeldy and Strimvelis in Europe, we will not achieve profitability unless and until we complete the development of, and obtain the regulatory approvals necessary to commercialize, additional product candidates. Our ability to generate future revenue from product sales depends heavily on our and or our collaborators' success in:

- completing research and pre-clinical development of our product candidates and identifying attractive new gene therapy product candidates;
- conducting and fully enrolling clinical trials in the development of our product candidates, including maintaining or reaching target enrollment levels and collecting the necessary follow-up data;
- seeking and obtaining regulatory and marketing approvals for product candidates for which we complete registrational clinical trials that achieve their primary endpoints;
- successfully commercializing Libmeldy in Europe and other 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 post-marketing commitments for regulatory compliance for Libmeldy and Strimvelis in the European Union;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors for Libmeldy and 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 Libmeldy and Strimvelis, if sales are resumed, and any of our product candidates for which we obtain marketing approval;
- obtaining market acceptance of Libmeldy and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- the impact of geopolitical instability and the ongoing COVID-19 pandemic, including the emergence of new variants;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and manufacturing capabilities;
- 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 expect that we will continue to incur significant costs associated with commercializing Libmeldy in Europe and any other products for which we obtain marketing approval. Our expenses could increase beyond expectations if the FDA, the EMA or

other regulatory authorities require us to perform clinical or 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 generate more significant revenue from sales of Libmeldy in Europe and generate revenue 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 not receive any additional amounts under the Securities Purchase Agreement, dated March 6, 2023.

As previously disclosed, on March 6, 2023, we announced a private placement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares and warrants. If certain conditions are met and all warrants are exercised, the Company could receive a total of $188 million pursuant to the private placement. In accordance with the Securities Purchase Agreement (the "SPA"), the Company received $34 million at the initial closing on March 10, 2023. However, the Company may not receive any additional amounts under the SPA.

As described below, the second closing is contingent and could be delayed or never happen, and certain of the contingencies are not entirely without the Company's control. In addition, the warrants sold under the SPA do not obligate the purchasers to exercise them, and even if they are exercised they are exercisable at a lower price if FDA approval of OTL-200 is delayed beyond 2024.

The investors in the private placement agreed to purchase additional ordinary shares, non-voting ordinary shares and warrants at a pre-agreed price at a second closing for an aggregate total of $34 million. The second closing is subject to the Company's public announcement of our intention to submit a BLA application with the FDA following receipt of minutes from the Company's pre-BLA meeting with the FDA, which is currently scheduled for the second quarter of 2023. The second closing is also subject to shareholder approval for authority under U.K. law to allot the shares issuable upon exercise of the warrants and to disapply pre-emption rights in respect of such authority.

The second closing has not yet occurred, and it may never occur. The minutes from our pre-BLA meeting with the FDA may advise us not to submit a BLA application without making certain changes or performing additional work. We could also decide that as a result of the pre-BLA meeting additional work is necessary or appropriate before submitting a BLA application. If either of these things were to occur, the second closing would be delayed and may not occur.

The second closing could also be delayed or never occur if the Company fails to receive the necessary shareholder approvals. Although we have agreed to hold a shareholder meeting no later than 120 days following the initial closing, the required shareholder votes could fail or we could fail to receive the quorum necessary to hold the vote. Under U.K. law, the proposal asking shareholders to disapply pre-emption rights is considered a special resolution requiring the affirmative vote of 75% of votes cast by shareholders present (in person or by proxy) at the meeting and entitled to vote. Under the SPA, we have agreed to continue seeking shareholder approval if the necessary votes fail for a period of time, but we may never receive the required shareholder vote.

The purchasers of warrants are not obligated to exercise the warrants, so we may not receive any additional proceeds from their exercise. The warrants will become exercisable during the 30 days following the Company's announcement of receipt of marketing approval of its BLA with respect to OTL-200; provided, that exercise of any warrant is conditioned on the receipt of shareholder approval (as described above). If the Company does not announce receipt of marketing approval of its BLA or does not receive the necessary shareholder approval, the warrants will expire on March 10, 2026. In addition, the exercise price of the warrants is lower if OTL-200 is approved by the FDA after 2024, so any proceeds we receive from their exercise could be lower than the total amount possible as of today. The exercise price of the warrants is $1.10 per ordinary share if OTL-200 is approved by the FDA in 2024 and $0.95 per ordinary share if approval comes after 2024.

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

Our operations have consumed a substantial amount of cash since our inception, and we recorded negative cash flows from operating activities during the twelve months ended December 31, 2022, primarily due to our net loss of $150.7 million for that period. We expect to continue to incur substantial expenses in connection with our ongoing activities, which may increase over time, particularly as we (i) continue to commercialize Libmeldy in Europe, (ii) continue the research and development of, initiate further clinical trials of and seek marketing approval for, our product candidates and (iii) continue to enhance and optimize our vector technology and manufacturing processes. In addition, we expect to incur significant expenses related to product sales, post-marketing regulatory commitments, medical affairs, marketing, manufacturing, distribution and quality systems to support Libmeldy and any other products for which we obtain marketing approval. Furthermore, we will continue to incur costs associated with operating as a public company, including with respect to the system and process evaluations and testing of our internal controls and financial reporting. 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, or at all, we would be forced to delay, reduce or eliminate certain of our ongoing activities, such as research and development programs and commercialization efforts.

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

- the success of our commercialization efforts and market acceptance of Libmeldy in Europe;
- the cost and our ability to maintain the commercial infrastructure and manufacturing capabilities to support Libmeldy in Europe and any other products for which we obtain marketing approval, including costs relating to quality systems, regulatory affairs, compliance, product sales, medical affairs, commercial marketing, manufacturing and distribution;
- qualifying for, and maintaining, adequate coverage and reimbursement by government and payors on a timely basis for Libmeldy 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 post-marketing commitments for regulatory compliance for any products for which we obtain marketing approval;
- the scope, progress, results and costs of drug discovery, laboratory testing, pre-clinical development and clinical trials for our product candidates or future product candidates, including the need to conduct long-term follow-up for up to 15 years for our development programs and additional clinical trials to support marketing approvals 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 Libmeldy 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 pre-clinical testing and clinical trials, as well as preparing for the potential commercialization of these product candidates, 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 Libmeldy and Strimvelis. In addition, Libmeldy and any other products for which we obtain and maintain marketing approval may not achieve commercial success. Any product revenue 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 additional indebtedness we incur would result in additional 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, alliances or 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. In the past several years, global credit and financial markets have experienced volatility, instability and disruptions, including as a result of the COVID-19 pandemic, geopolitical instability and other macroeconomic factors. The significant volatility in public equity markets and the disruptions to the U.S. and global economies may make it more difficult to raise capital through sales of our ADSs on favorable 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 pre-clinical 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 commercialization of Libmeldy. Consequently, any predictions about our future success or viability may not be as accurate as they might 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.

Unfavorable market and global economic conditions could adversely affect our business, financial condition or results of operations.

As widely reported, global credit and financial markets have experienced extreme volatility and disruptions in the past several years, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, and uncertainty about economic stability, including most recently in connection with the ongoing COVID-19 pandemic, current macroeconomic conditions, currency exchange rates, and volatile financial markets. There can be no assurance that further deterioration in credit and financial markets and confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. Furthermore, our stock price may decline due in part to the volatility of the stock market and the general economic downturn.

Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay, scale back or discontinue the development and commercialization of one or more of our product candidates or delay our pursuit of potential in-licenses or acquisitions. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive these difficult economic times, which could directly affect our ability to attain our operating goals on schedule and on budget.

Volatility among foreign currencies could impact our results of operations. As an example, we had net realized and unrealized losses on foreign currency transactions of $24.4 million during the twelve months ended December 31, 2022, compared to net realized and unrealized losses of $1.2 million during the twelve months ended December 31, 2021. Unrealized gains and losses are driven primarily by entities that have a functional currency other than the U.S. Dollar that have intercompany balances denominated in U.S. Dollar.

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 Libmeldy, we may experience delays in establishing a sustainable, reproducible and scalable manufacturing capability with commercial CDMO 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 the process 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. 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, Europe or in other jurisdictions, or how long it will take to commercialize Libmeldy in Europe or 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.

The results from our clinical trials for OTL-200 for MLD and for any of our other product candidates may not be sufficiently robust to support marketing approval or the submission of marketing approval. Before we submit our product candidates for marketing approval, the FDA 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 may not be sufficiently robust to support the approval of or submission of marketing approval for our product candidates, including by the FDA for OTL-200. The FDA and EMA normally require two registrational trials to approve a drug or biologic product, and therefore either the FDA or EMA might require that we conduct additional clinical trials of our product candidates prior to a BLA or MAA submission, respectively. The FDA and EMA typically do not consider a single registrational clinical trial to be adequate to serve as sufficient evidence to support a marketing authorization unless, among other things, (i) the trial is well-controlled and demonstrates a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with a potentially serious outcome and (ii) a confirmatory study would be practically or ethically impossible.

Due to the nature of the indications our product candidates are designed to treat, and the limited number of patients with these conditions, a placebo-controlled and blinded study is not always practicable for ethical and other reasons. Accordingly, in some cases our registrational programs rely on natural history models to demonstrate clinical efficacy. While the FDA recognizes the potential for natural history models to alleviate the need for placebo arms in trials for drugs that target very rare diseases, 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. It is possible the FDA will not consider our comparisons to natural history data and, where available, historical transplant data or intra-subject comparison between before gene therapy and after gene therapy, to provide clinically meaningful results. Additionally, even though OTL-200 for MLD has achieved the primary endpoints in its ongoing registrational clinical trial, the FDA has not yet approved the clinical meaningfulness of the trial results and their sufficiency to support a marketing authorization.

For example, although the FDA cleared our IND application for OTL-200 in 2020 and we received Regenerative Medicine Advanced Therapy, or RMAT, designation in 2021, there can be no guarantee we will be successful in resolving open matters to the FDA's satisfaction before our intended BLA submission. We continue to engage with the FDA as we seek to address its recommendations and identify expeditious paths to market for our product candidates.

It is possible that the FDA or EMA may recommend or require us to conduct further studies, analyses or registrational trials with respect to our product candidates, possibly involving a larger sample size or a different clinical trial design. 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 a BLA or MAA submission, as applicable.

In addition, data obtained from pre-clinical 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. The FDA may further refer any future BLA submission to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. This review may add to the time for approval, and although the FDA is not bound by the recommendation of an advisory committee, objections or concerns expressed by the advisory committee may cause the FDA to delay or deny approval. We also may experience regulatory delays or rejections as a result of many factors, including serious adverse events, or 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 pre-clinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications.

It is possible that the FDA or EMA may not consider the results of our clinical trials, including reliance on foreign clinical data, to be sufficient for approval of our product candidates. If the FDA or EMA require 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 EMA may have divergent opinions on the elements necessary for a successful BLA and MAA submission, respectively, which may cause us to alter our development, regulatory or commercialization strategies.

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 Therapeutic Products 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. The NIH has refocused the NIH Recombinant DNA Advisory Committee and changed its name to the Novel and Exceptional Technology and Research Advisory Committee, or NExTRAC. NExTRAC is a federal advisory committee that provides recommendations to the NIH Director and a public forum for the discussion of the scientific, safety, and ethical issues associated with emerging biotechnologies, which include, but are not restricted to, technologies surrounding advances in recombinant or synthetic nucleic acid research such as human gene transfer. 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.

The FDA 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 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. 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 pre-clinical 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 pre-clinical 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.

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 might be materially and adversely affected.

The FDA and EMA have released a series of final guidance documents and a draft guidance document for consultation, which among 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.

Libmeldy, Strimvelis and our product candidates and the process for administering Libmeldy, Strimvelis and our 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 -- have 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.

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 (or oncogenesis) by the vectors, leading to malignant transformation of transduced cells. There have been several adverse events and 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. In October 2020, we were notified that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with lymphoid T cell leukemia. Subsequent findings confirmed that the patient's leukemia was due to insertional oncogenesis attributable to treatment with Strimvelis. The EMA's Committee for Medicinal Products for Human Use, or CHMP, concluded that the risk-benefit balance remains favorable and requested that the Strimvelis product information identify insertional mutagenesis (or oncogenesis) as an "important identified risk" instead of an "important potential risk" in light of this event.

Strimvelis is the only gammaretroviral vector-based gene therapy in our portfolio. Libmeldy and all of our pipeline therapies employ the self-inactivating (SIN) lentiviral vector-based approach, which has been specifically designed to avoid insertional oncogenesis after administration. Although to our knowledge and as of the date of this report no evidence of insertional oncogenesis has been observed with lentiviral vector-based HSC gene therapy in any of our programs, there can be no assurance that this will continue to be the case. Moreover, 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, 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. Other non-U.S. regulatory

authorities could impose other specific obligations, such as through a risk management plan, or RMP, submitted to the EMA. Furthermore, if we or others later identify undesirable side effects caused by Strimvelis, Libmeldy or our 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 Libmeldy 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 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 CDMOs 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 CDMOs, and we cannot provide assurances that we will satisfy such comparability requirements. 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 Great Osmond Street Hospital, or 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, bacteremia, was observed in the clinical trial conducted at University of California Los Angeles, or UCLA, for our since-returned program OTL-101 for ADA-SCID with the fresh drug product manufactured at the academic facility, also possibly due to contamination of the drug product. The bacteremia resolved on day three without sequelae. We believe that our commercial manufacturing processes for our 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 contamination of products that might have resulted in 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 CDMOs prior to granting any marketing approval, which could delay clinical development or marketing approval of our product candidates.

We may be unable to demonstrate comparability between (i) 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, (ii) drug product that has been cryopreserved and fresh drug product, and (iii) the manufacturing process used at academic centers with the manufacturing process used at CDMOs. Failure to demonstrate such comparability could affect our ability to secure regulatory approval for our product candidates or could affect the commercial viability of our product candidates if approved for use using only HSCs derived from bone marrow or using only 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 CDMOs 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 or drug product manufactured at academic research centers, we will need to demonstrate comparability between vector and drug product manufactured by our CDMOs with vector 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. In other 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 studies (including comparability analyses), pre-clinical studies or clinical trials before approving our product candidates using these intended commercial production methods and processes. Moreover, we cannot be assured that our analytical comparability analyses or clinical trials will be sufficiently robust to support approval of our product candidates using these production methods and processes.

If any of the FDA, EMA or other regulatory authority does not accept our comparability data or if an adequate potency assay for a product candidate is not available or supported by such regulatory authority, 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 regulators with satisfactory comparability data, which may include data from additional clinical trials or require additional test method development. Potency assays that measure strength (e.g., enzymatic activity, or other relevant function) of each active ingredient are required for release testing of licensed biological drug products, comparability and stability analysis.

If an adequate potency assay for a product candidate is not available, if we face delays, or if the FDA or EMA require additional tests or recommend a different approach to support the potency of any of our product candidates, regulatory approval for any such product candidates will be delayed and such regulators might request additional clinical data to support comparability analysis. 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, any regulatory approval would be limited to drug product manufactured with HSCs derived from the patient's bone marrow until we are able to provide the regulators with satisfactory comparability data, which may include data from additional clinical trials.

Our development and commercialization efforts, respectively, may be unsuccessful.

We may spend several years and devote substantial resources to any particular current or future product candidate, and failure may occur at any stage. Further, even if we receive approval of a product candidate, we may not achieve commercial success for a variety of facts. For example, we may not achieve market acceptance in the medical community, our pricing assumptions might be wrong, and our assumptions about the size of the anticipated patient populations may prove inaccurate.

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. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for treatment of adenosine deaminase severe combined immunodeficiency, or ADA-SCID, and OTL-300 for treatment of Beta-thalassemia, or TDT. We have since returned licenses to the original licensors relating to both programs. Additionally, in March 2022, we announced that we would discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich Syndrome, or WAS, OTL-102 for treatment of X-linked chronic granulomatous disease, or X-CGD, and Strimvelis.

Our focus on the advancement of our other product candidates may ultimately prove to be unsuccessful or less successful than if we had continued to prioritize such de-prioritized product candidates, and if we choose to re-prioritize such de-prioritized product candidates in the future, we may experience delays that would not have otherwise occurred, due to inefficiencies from loss of organizational knowledge and ramp up costs. Moreover, we may be unable to realize the savings we expect to achieve by de-prioritizing certain programs, which could result from, among other things, higher than expected transition or termination costs.

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.

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 bone marrow transplantation or enzyme replacement therapy. We 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.

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 Libmeldy, raise capital, expand our business or continue our operations.

Interim data and ad hoc analyses are preliminary in nature. Success in pre-clinical studies or early clinical trials may not be indicative of results obtained in later trials.

From time to time, we may publish interim data 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 longer-term 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 occasionally 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 University College London, UCLA, Telethon-OSR 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 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 pre-clinical 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 pre-clinical 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 pre-clinical 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 Libmeldy (OTL-200), follow-up in 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 provide adequate support for marketing approvals by the FDA, in the case of Libmeldy, without conducting further clinical trials. 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 are limited data concerning long-term safety and efficacy following treatment with our product candidates. Our product candidates may fail to adequately demonstrate safety and efficacy in clinical development despite positive results in pre-clinical 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 pre-clinical 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 regulatory framework and related requirements, regulatory authorities may not accept compassionate use data as sufficiently robust clinical evidence 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 generally, competitive clinical trials for similar patient populations, clinical trials in product candidates employing our vectors, the existence of current treatments or for other reasons. Additionally, the COVID-19 global pandemic has had and may continue to have a sustained impact on our ability to recruit and follow-up with patients either due to continued or renewed restrictions on travel or shelter-in-place orders or policies or due to changes in patient willingness to participate in trials or travel to study sites in the wake of the pandemic. Additionally, COVID-19 related study site policies may create delays or setbacks in our ability to continue to enroll or to dose patients. 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 pre-treatment 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;
- the impact of the COVID-19 global pandemic or future pandemics or similar events on patients’ willingness and ability to participate in clinical trials or on study site policies;
- 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 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 the outcome is uncertain. 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 Institutional Review Board, or IRB, approval at each clinical trial site;
- delays in recruiting suitable patients and in sufficient volume 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 record keeping 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;
- delays in patient enrollment, missed assessments resulting from remote follow-up visits, or delays in completion of participation as a result of the impact of the COVID-19 global pandemic or future pandemics or similar events;
- 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 pre-clinical and clinical development could result in additional costs to us or impair our ability to generate revenue. 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 (or equivalent requirement from a non-U.S. regulatory authority) 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 (or equivalent requirement from a non-U.S. regulatory authority);
- 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.

Even if we complete the necessary pre-clinical 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 narrower indication than we seek.

We cannot commercialize a product until the appropriate regulatory authorities have reviewed and approved such product candidate. Even if a product candidate demonstrates 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 pre-clinical 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. We could also face delays if regulatory authorities are unable to complete required inspections, which could occur for reasons outside of our control, such as travel restrictions.

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, 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 or use of different manufacturing facilities) than we are seeking. If we are delayed in obtaining or unable to obtain necessary regulatory approvals, or if we obtain more limited regulatory approvals than we expect, our business, prospects, financial condition and results of operations may suffer.

Even if we complete the necessary pre-clinical 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, record keeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA, other regulatory agencies in the United States, 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 only limited experience in submitting and supporting the applications necessary to gain marketing approvals, and we expect to rely on third-party CROs to assist us in this process.

Securing marketing approval requires the submission of extensive pre-clinical 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, 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 pre-clinical, clinical or other studies. In addition, varying interpretations of the data obtained from pre-clinical 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 revenue will be materially impaired.

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. For example, though we received standard marketing authorization of Libmeldy (OTL-200) from the European Commission in December 2020, there is no guarantee that we will receive approval from 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 pre-clinical 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 may be harmed.

Additionally, the UK formally left the EU in January 2020. The EU and the UK have concluded a Trade and Cooperation Agreement, or TCA, which has been formally applicable since May 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP, inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations. At present, Great Britain has implemented EU legislation on the marketing, promotion and sale of medicinal products through the Human Medicines Regulations 2012 (as amended) (under the Northern Ireland Protocol, the EU regulatory framework will continue to apply in Northern Ireland). The regulatory regime in Great Britain therefore currently aligns in the most part with EU regulations, however it is possible that these regimes will diverge in the future now that Great Britain's regulatory system is independent from the EU and the TCA does not provide for mutual recognition of UK and EU pharmaceutical legislation. For example, the new Clinical Trials Regulation, which became effective in the EU on January 31, 2022, and provides for a streamlined clinical trial application and assessment procedure covering multiple EU Member States, has not been implemented into UK law, and a separate application will need to be submitted for clinical trial authorization in the UK. The separate, and potentially diverging, regulatory regimes between Great Britain and the EU may increase our regulatory burden of applying for and obtaining authorization in Great Britain and the EU.

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 have been conducted outside the United States. Although the FDA may accept data from clinical trials conducted outside the U.S., 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 data from any trial that we conduct outside the U.S., due to study design or otherwise, 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. Further, if we do not have an IND open for a product candidate, we forego more frequent interactions and dialogue with the FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of such product candidates later in development should the FDA later disagree with the design or conduct of our trials or product comparability approach.

In addition, in order to commence a clinical trial in the U.S., 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 be required to conduct additional pre-clinical 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.

While we intend to seek designations for our product candidates with the FDA and other comparable 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-200 for MLD received RMAT designation from the FDA, and OTL-203 for MPS-IH received a Priority Medicines, or PRIME, designation from EMA. Despite these designations, there can be no assurance that we will successfully obtain these or other designations for any of our other product candidates. In addition, while such designations could expedite the development or review 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, we may seek RMAT designation for some of our other 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.

In addition, the FDA has granted Rare Pediatric Disease designation to OTL-200 for MLD, OTL-201 for MPS-IIIA and OTL-203 for MPS-IH, 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 through September 30, 2024, with potential for PRVs to be granted through September 30, 2026. This program has been subject to criticism, including by the FDA, and it is possible that even if we obtain approval for Libmeldy (OTL-200), OTL-201 for MPS-IIIA and OTL-203 for MPS-IH 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.

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 certain product candidates, including Libmeldy, 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 certain product candidates. 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 Libmeldy (OTL-200) and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-203 for MPS-IH from the FDA, but we may be unable to obtain orphan drug designation for our other product candidates. 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 EU, the EMA's Committee for Orphan Medicinal Products grants orphan designation in respect of a medicinal product if the sponsor can establish that such product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in 10,000 persons in the EU. Additionally, orphan designation may be 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 such products would generate sufficient return in the EU to justify the necessary investment their development. In either case, the applicant for orphan designation must also demonstrate that no satisfactory method of diagnosis, prevention, or treatment for the condition has been authorized for marketing in the EU (or, if a method exists, the new product would be a significant benefit to those affected by the condition).

We have sought and received orphan drug designation for Libmeldy and OTL-201 for MPS-IIIA from the FDA and EMA and for OTL-203 for MPS-IH from the FDA. 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 other 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 EU. The exclusivity period in the EU can be reduced to six years if a product no longer meets the criteria for orphan designation, including 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 EU, a 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.

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, where the benefit of immediate availability of the medicine outweighs the risk inherent in the fact that additional data are still required or in the interests of public health. In such cases, it is possible for the 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 post-authorization;
- 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 pre-clinical 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.

Libmeldy 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. For example, as a post-marketing commitment, we are continuing to follow patients in the OTL-200 clinical development program for up to 15 years, and data will be presented to regulators at agreed points in order to further characterize the long-term efficacy and safety of Libmeldy.

Any regulatory approvals that we receive for our product candidates also may be subject to a REMS or equivalent requirement from a non-U.S. regulatory authority, 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 long-term safety and efficacy follow-up for as long as 15 years post therapy. The holder of an approved BLA must also 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 EU, the advertising and promotion of our products are subject to EU laws governing promotion of medicinal products, interactions with physicians, misleading and comparative advertising and unfair commercial practices. In addition, other legislation adopted by individual EU 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 EU. The applicable laws at EU level and in the individual EU 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 EU 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 EU Member States both before and after grant of the manufacturing and marketing authorizations. This includes 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 EU laws and the related national laws of individual EU Member States governing the conduct of clinical trials, manufacturing approval, marketing authorization of medicinal products, both before and after the grant of a marketing authorization, and marketing of such products following the grant of an 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, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that the EMA and the competent authorities of the EU 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 a marketing authorization or imposition of financial penalties or other enforcement measures.

Risks related to manufacturing and supply

Gene therapies are novel, complex and difficult to manufacture. We have limited manufacturing experience, and we rely on third party manufacturers that are often our single source of supply. We could experience manufacturing problems that result in delays in the development or commercialization of our commercial products 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. Libmeldy, 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, each manufacturing batch must meet certain analytical specifications to be released and 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 CDMOs for the manufacture of our viral vectors and drug product. We expect these CDMOs will be capable of providing sufficient quantities of our viral vectors and gene therapy products to meet the anticipated scale of our clinical trials and current and initial commercial demands, if any additional products are 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 develop in-house capabilities. We believe that there are alternate sources of supply that can satisfy our clinical and commercial requirements; however, identifying and establishing relationships with such sources, if necessary, could result in significant delays or material additional costs, which 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 our CDMOs 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 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 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 CDMOs' 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 a CDMO facility, 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; therefore, the time frame required for us to obtain such approval is uncertain. In addition, we must pass a pre-approval inspection of our CDMOs 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, CDMOs and suppliers. If any of our vendors, contract laboratories, CDMOs 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 spend 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.

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 complex supply chain or satisfying manufacturing-related regulatory requirements.

The FDA, 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, 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.

Managing an autologous ex vivo gene therapy supply chain is highly complex. We must identify, engage and coordinate with treatment centers where a patient's cellular source material must be collected, prepared, stored and transported to the manufacturing facility and the cryopreserved drug product must be returned to the treatment center for administration into the patient using controlled temperature shipping containers.

Once collected from the patient, the cellular source material must be prepared and stored according to specified procedures. While we intend to standardize the processes at treatment centers, if there is a deviation of the processes, the cellular source material from a patient could be adversely impacted and potentially result in manufacturing failures. The patient's cellular materials must be transported to the manufacturing facility using a shipping container that maintains the material at a cool temperature and must typically be delivered and processed 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, being held up at a customs point, COVID-19 impacts or other events, 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, being held up at a customs point, COVID-19 impacts 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.

We may be delayed or unable to identify, engage, successfully coordinate or qualify with treatment centers in the regions we are targeting as part of our commercial strategy, which could delay or prevent patients from receiving gene therapy treatments, if approved. If our treatment centers fail to perform satisfactorily, we may suffer reputational, operational, and business harm.

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.

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.

Interruptions in the supply of viral vectors 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 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, due to transportation or other delays, including delays or disruptions resulting from the impact of the COVID-19 pandemic, 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 products 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 under controlled temperature conditions 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 we may, enter into collaborations with third parties to develop or commercialize product candidates. These collaborations may not be successful.

We have entered into licensing and collaboration agreements with third parties, including the GSK Agreement, pursuant to which GSK transferred several programs to us, including Strimvelis and Libmeldy (OTL-200). In addition, GSK novated to us its research and collaboration 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.

There could also be disagreements as to whether certain amounts are payable under our licensing and collaboration agreements. For example, there could be disputes as to whether certain milestone payments have been triggered. Such disputes would divert management attention, could harm our relationship with our collaborators or licensors, and could lead to payments that we do not currently anticipate.

We also entered into a collaboration with Pharming Group N.V., or Pharming, pursuant to which Pharming was granted worldwide rights to OTL-105, an investigational ex vivo autologous hematopoietic stem cell gene therapy for the treatment of hereditary angioedema. The Company will lead the completion of IND-enabling activities and oversee manufacturing of OTL-105 during pre-clinical and clinical development, which will be funded by Pharming.

We may 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 revenue 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.

Any 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 payments, under our collaborations, including milestones 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 such collaborations. 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.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of 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 will likely be time-consuming and complex. Our ability to reach a definitive collaboration agreement in such instances 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 additional 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.

We are not able to independently manufacture material for our planned clinical programs or our commercial supply of Libmeldy or any other product for which we obtain marketing approval, if any, and we do not expect to be able to in the foreseeable future. We currently rely on our CDMOs and in some cases academic partners for the production of our viral vectors and product candidates for our ongoing registrational and clinical trials and pre-clinical studies. For future clinical

trials and for Libmeldy and other products for which we obtain marketing approval, if any, we intend to utilize materials manufactured by CDMOs. If our academic partners or these CDMOs 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 CDMOs, we will not be able to complete, or may be delayed in completing, the pre-clinical 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 pre-clinical data. In such instances, we may need to enter into an appropriate third-party relationship, which may not be readily available or available on acceptable terms. This could cause additional delay or increased expense prior to the approval of our product candidates and could have a negative impact on our business, financial condition, results of operations and prospects.

We partner with CDMOs and intend to utilize viral vectors and gene therapy products manufactured by CDMOs 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 CDMOs, 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 CDMOs, 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 CDMOs 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 to produce our product candidates. Furthermore, demand for CDMO 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 CDMOs may terminate their engagements with us. If we need to enter into alternative arrangements, it could delay our development activities. Our reliance on our CDMOs 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 CDMOs, we may rely on additional third parties to manufacture our viral vectors or drug products in the future and to perform quality testing. Reliance on these third parties entails risks that we would not be subject to if we manufactured the product candidates ourselves, including:

- reduced control for certain aspects of manufacturing activities;
- termination or non-renewal 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 or future pandemics or disruptions.

Any of these events could lead to clinical trial delays, 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 pre-clinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing pre-clinical and clinical programs. 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 pre-clinical 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 GLP and GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the 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. The FDA, EMA or comparable foreign regulatory authorities may deem the clinical data generated in our clinical trials unreliable and may require us to perform additional clinical trials before approving our marketing applications if, among other things, we fail to exercise adequate oversight over any of our academic partners or CROs or if our academic partners or CROs do not successfully carry out their respective 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. 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 revenue 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-201 for MPS-IIIA, OTL-203 for MPS-IH or any other product candidate investigated in an academic-sponsored clinical trial. 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 first-hand 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 pre-clinical, manufacturing or clinical data generated by these academic-sponsored trials or our interpretation of pre-clinical, manufacturing or clinical data from these academic-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional pre-clinical, 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 products. 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 CDMOs 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 CDMOs 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 cGMP and other applicable regulations that are enforced through facilities inspection programs. Some of our CDMOs have not produced a commercially-approved product and have never been inspected by the FDA or other regulatory body. Our quality systems and the facilities and quality systems of some or all of our CDMOs 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 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 CDMOs 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 products or product candidates, if approved, and 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 pre-clinical 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;
- interruptions, shortages, delivery delays and potential discontinuation of supply as a result of the ongoing COVID-19 global pandemic, or any recurrence of the pandemic or future pandemics; 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 products 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 such third parties. 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

If we are unable to either establish effective sales and marketing capabilities or enter into agreements with third parties for such services, we may be unable to generate product revenue.

We are working to successfully commercialize Libmeldy in Europe, and we intend to commercialize our product candidates, if approved, in the United States, Europe and other markets. Given the relative rarity of the indications that we are targeting, we are commercializing Libmeldy, and we currently intend to commercialize any product candidates that are approved, directly with specialized teams. We currently have a limited marketing and sales team, and we must build and expand our commercial infrastructure and capabilities or make arrangements with third parties to perform those services. If we are unable to do so, we may be unable to generate sufficient revenue to sustain our business.

Regardless of whether we establish our own sales and marketing capabilities or enter into third-party arrangements, there are risks involved. On the one hand, recruiting and training a commercial organization is both expensive and time consuming, and we could face delays in any product launch. If a product launch is delayed or does not occur, we may be unable to recoup our investment if we cannot retain or reposition our sales and marketing personnel. There are several factors that could inhibit our efforts to commercialize Libmeldy and our product candidates, if approved, on our own. These include, but are not limited to:

- we may be unable to recruit, train and retain adequate numbers of effective sales and marketing personnel;

- our sales personnel may be unable to obtain access to physicians or may be unable to persuade adequate numbers of physicians to prescribe Libmeldy and any future products that we may develop;
- we may face changes or setbacks at treatment centers contracted for the administration of any approved treatments;
- adverse events could occur;
- we are unable to offer complementary treatments, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- we may experience unforeseen costs and expenses associated with creating an independent sales and marketing organization.

In addition, we will need to commit significant additional management and other resources to maintain and grow our sales organization. We may not be able to achieve the necessary development and growth in a cost-effective manner or realize a positive return on our investment.

On the other hand, there are risks with entering into third party arrangements for the performance of sales, marketing and distribution services. These include, but are not limited to:

- our product revenue or the profitability to us from these revenue streams may be lower than if we were to perform these services ourselves;
- we may be unable to enter into suitable third-party arrangements or we may only be able to do so on unfavorable terms, particularly given that we face competition in any search for third-party assistance; and
- we will likely have limited control over third parties, and they may fail to devote the necessary resources and attention to market and sell our products or product candidates, if approved, effectively.

If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may be unable to generate product revenue.

We face significant competition in our industry and there can be no assurance that our commercial products or 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, including new areas that we may target as part of our strategic initiatives.

We rely primarily on know-how and trade secret protection for aspects of our proprietary technologies, Libmeldy and our product candidates. This means that barriers to entry that typically apply in the case of pharmaceutical and biopharmaceutical companies with issued patents covering aspects of their proprietary technologies, products and product candidates, such as composition of matter claims, will generally not apply to our commercial products or our product candidates, and this may expose us to 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 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 therapy approach, and these competitive approaches may be comparable or superior to our approach. One or more of these companies may seek to develop products that compete directly with our commercial products or one or more of our product candidates, the result of which could have a material adverse effect on our business. 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.

If the size and value of the market opportunities for our commercial products or product candidates are smaller than our estimates, or if we have difficulty in finding patients that meet eligibility requirements for Libmeldy or any of our product candidates, if approved, our product revenue may be adversely affected and our business may suffer.

We focus our research and product development on treatments for immunological disorders and inherited neurometabolic and neurodegenerative genetic disorders. We base our market opportunity estimates on a variety of factors, including our estimates of the number of people who have these diseases, the potential scope of our approved product labels, the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, various pricing scenarios, and our understanding of reimbursement policies for rare diseases in particular countries. These estimates are based on many assumptions and may prove to be incorrect, and new studies may reduce the estimated incidence or prevalence of these diseases. Estimating market opportunities can be particularly challenging for ultra-rare indications, such as the ones we currently address, as epidemiological data is often more limited than for more prevalent indications and can require additional assumptions to assess potential patient populations. For example, as we advance our product candidates towards commercialization, learn more about market dynamics and engage with regulators on potential marketing approvals, our view of the initial potential market opportunity for our products will become more refined. In some cases, the approved label may initially be directed to a narrower patient population with the opportunity to expand the label upon submission of additional clinical data. For example, in the case of Libmeldy, we are initially focused primarily on annual incidence of the disease. This means the initial market opportunity for Libmeldy may be smaller than the total addressable market opportunity that could be achieved over time. If we are unable to advance product candidates with attractive market opportunities, our future product revenue may be smaller than anticipated and our business may suffer. Patient identification efforts also influence the ability to address a patient population. If efforts in patient identification are unsuccessful or less impactful than anticipated, for instance, because of a lack of newborn screening or diagnostic initiatives, inadequate disease awareness among healthcare providers, or otherwise, we may not address the entirety of the opportunity we are seeking. As a result, patients may be difficult to identify and access, the addressable patient population in the United States, Europe and elsewhere may turn out to be lower than expected, or patients may not be otherwise amenable to treatment with our products, 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 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 pre-clinical 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. In the United States and markets in other countries, patients generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. 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 covered and 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. If coverage and adequate reimbursement are not available, or are available only to limited levels, we may not be able to successfully commercialize our product candidates. 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.

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. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the reimbursement rate that the payor 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.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, the principal decisions about coverage and 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, or HHS. 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. Factors payors consider in determining reimbursement are based on whether the product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

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 revenue from sales by us or our collaborators, and the potential profitability of our drug products, in those countries would be negatively affected. Some countries may also require the completion of clinical trials that compare the cost effectiveness of a particular product candidate to currently available therapies. 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 revenue we are able to generate from the sale of the product in that particular country. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our product candidates. Historically, products launched in the European Union do not follow price structures of the U.S. and generally prices tend to be significantly lower.

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 products, if approved, 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.

Risks related to our business operations

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. Adverse events in other lentiviral gene therapy trials unrelated to our product candidates could negatively impact our business. 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. 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. Media attention to individual patients' expanded access requests has resulted in the introduction and passage of legislation at the local and national level referred to as "Right to Try" laws, which are intended to help enable patient 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 in May 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. This could cause significant delays or an inability to successfully commercialize our product candidates, which could materially harm our business.

We may be unable to effectively manage our programs.

In some instances we may decide to discontinue our investment in programs after we've invested time and capital into such programs. For example, in May 2020, we announced a reduction of the investment in and scope of OTL-101 for ADA-SCID and OTL-300 for TDT, and we have since returned licenses for both programs to the licensor. Additionally, in March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis, OTL-103 for treatment of WAS and OTL-102 for treatment of X-CGD. We may in the future decide to discontinue additional programs, and we may incur transition and termination costs. In addition, we may in the future decide to expand our operations to different territories and indications, including through in-licenses. Managing these expanded operations will pose challenges for us, and we cannot assure that we will be successful.

We face potential product liability.

The use of our product candidates in clinical trials and the sale of Strimvelis and Libmeldy 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. 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 as appropriate if and as we commercialize additional products, but 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.

An information security incident, including a cybersecurity breach, could have a negative impact to the Company's business or reputation.

Security incidents have become more prevalent across industries and may occur on our systems or on the systems of our third-party service providers. These security incidents may be caused by, or result in, security breaches, computer malware or malicious software, ransomware, computer hacking, denial of service attacks, security system control failures in our own systems or from service providers we use, email phishing, software vulnerabilities, social engineering, sabotage, drive-by downloads and the malfeasance of our or our service providers' employees, among other things. We have taken measures to detect, remediate and prevent future attacks and security threats. However, we may be affected, particularly given that such attacks are increasing in volume and sophistication and attack techniques frequently change.

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, among other things, damage from computer viruses, unauthorized access, ransomware, natural disasters, terrorism, war and telecommunication and electrical failures. Furthermore, the ongoing COVID-19 pandemic and the related disruptions to our business and our collaborators', contractors' and consultants' businesses may increase the risk of security incidents. 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 the 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.

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 our President & Chief Operating 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 qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. 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 pre-clinical 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 key employee or advisor could harm our business.

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, CROs and CDMOs. It is not always possible to identify and deter misconduct by employees and other third parties, 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. Misconduct by these parties could include intentional failures to (i) comply with the regulations of the FDA, EMA or of other foreign regulatory authorities, (ii) provide accurate information to the FDA, EMA and other foreign regulatory authorities, (iii) comply with healthcare fraud and abuse laws and regulations in the United States and abroad, (iv) report financial information or data accurately or (v) 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 such as criminal and administrative penalties, damages, imprisonment, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

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.

Successful commercialization of our products depends, in part, on the availability of reimbursement for such products in the markets where we sell our products. Governmental health authorities, private health insurers and other organizations are focused on controlling healthcare costs, and these methods are not always specifically adapted for new technologies, such as gene therapy and therapies addressing rare diseases. Legislative and regulatory action affecting reimbursement could impact our ability to sell our products profitably.

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 or impose price controls may adversely affect:

- the demand for our products, if approved;
- our ability to set a sufficient price;
- our ability to generate revenue and achieve or maintain profitability; and
- the level of taxes that we are required to pay.

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.

We are subject to the UK 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 below:

- 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. Violations are subject to civil and criminal fines and penalties for each violation, plus up to three times the remuneration involved, imprisonment, and exclusion from government healthcare programs. 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 whistle blower 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 or knowingly concealing or knowingly and improperly avoiding or decreasing an obligation to pay money to the federal government. Manufacturers can be held liable under the federal False Claims Act even when they do not submit claims directly to government payors if they are deemed to "cause" the submission of false or fraudulent claims. The federal False Claims Act also permits a private individual acting as a "whistle blower" to bring actions on behalf of the federal government alleging violations of the federal 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.
- 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, or HITECH and their respective implementing regulations, including the Final Omnibus Rule published in January 2013, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates, independent contractors or agents of covered entities, that perform services for them that involve the creation, maintenance, receipt, use, or disclosure of,

individually identifiable health information relating to the privacy, security and transmission of individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys' fees and costs associated with pursuing federal civil actions. In addition, there may be additional federal, state and non-U.S. laws which govern the privacy and security of health and other personal information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

- The U.S. federal transparency requirements under the ACA, including the provision commonly referred to as the Physician Payments Sunshine Act, and its implementing regulations, 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 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. Effective January 1, 2022, these reporting obligations extend to include transfers of value made to certain non-physician providers such as physician assistants and nurse practitioners.
- The federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs.
- The federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- Many states in the United States have enacted laws that regulate the privacy and security of certain types of personal information. For example, in California, the California Consumer Protection Act (CCPA), which went into effect on January 1, 2020, establishes a new privacy framework for covered businesses by creating an expanded definition of personal information, establishing new data privacy rights for consumers in the State of California, imposing special rules on the collection of consumer data from minors, and creating a new and potentially severe statutory damages framework for violations of the CCPA and for businesses that fail to implement reasonable security procedures and practices to prevent data breaches. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability. Some observers have noted that the CCPA could mark the beginning of a trend toward more stringent privacy legislation in the U.S., which could increase our potential liability and adversely affect our business.
- Additionally, a new California ballot initiative, the California Privacy Rights Act, or "CPRA," was passed in November 2020. The CPRA imposes additional obligations on companies covered by the legislation and will significantly modify the CCPA, including by expanding consumers' rights with respect to certain sensitive personal information. The CPRA also creates a new state agency that will be vested with authority to implement and enforce the CCPA and the CPRA. The effects of the CCPA and the CPRA are potentially significant and may require us to modify our data collection or processing practices and policies and to incur substantial costs and expenses in an effort to comply and increase our potential exposure to regulatory enforcement or litigation.
- Certain other state laws impose similar privacy obligations, and we also expect anticipate that more states to may enact legislation similar to the CCPA, which provides consumers with new privacy rights and increases the privacy and security obligations of entities handling certain personal information of such consumers. The CCPA has prompted a number of proposals for new federal and state-level privacy legislation. Such proposed legislation, if enacted, may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment of resources in compliance programs, impact strategies and the availability of previously useful data and could result in increased compliance costs or changes in business practices and policies.
- Following the UK's withdrawal from the EU, the EU GDPR was incorporated into UK domestic law. UK-based organizations doing business in the EU will need to continue to comply with the EU GDPR and now also the UK GDPR. The UK is now regarded as a third country under the EU GDPR, but the European Commission has issued a decision recognizing the UK as providing adequate protection under the EU GDPR ("Adequacy Decision"). Therefore, transfers of personal data originating in the EU to the UK remain unrestricted. The UK Government has also confirmed that transfers of personal data originating in the UK to the EU may continue to flow freely. The UK Government has also now introduced a Data Protection and Digital Information Bill ("UK

Bill") into the UK legislative process. The aim of the UK Bill is to reform the UK's data protection regime following Brexit. If passed, the final version of the UK Bill may have the effect of further altering the similarities between the UK and EEA data protection regime and threaten the UK Adequacy Decision from the EU Commission. This may lead to additional compliance costs and could increase our overall risk. The respective provisions and enforcement of the EU GDPR and UK GDPR may further diverge in the future and create additional regulatory challenges and uncertainties.

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 payor. 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 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 and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the GDPR also govern the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts. 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.

In the event we decide to conduct additional clinical trials or continue to enroll subjects in our ongoing or future clinical trials, we may be subject to additional privacy restrictions. The collection, use, storage, disclosure, transfer or other processing of personal data regarding individuals in the EEA or the UK, including personal health data, is subject to the GDPR. The GDPR is wide-ranging in scope and imposes numerous requirements on companies that process personal data, including requirements relating to processing health and other sensitive data, where required obtaining consent of the individuals to whom the personal data relates, providing information to individuals regarding data processing activities, implementing safeguards to protect the security and confidentiality of personal data, where required providing notification of data breaches, and taking certain measures when engaging third-party processors, including concluding data processing agreements, where required appointing data protection officers, where required conducting data protection impact assessments, and record-keeping. The GDPR also imposes strict rules and restrictions on the transfer of personal data to countries outside the EEA or the UK, including the United States (see below), and permits data protection authorities to impose large penalties for violations of the GDPR, including potential fines of up to €20.0 million (£17.5 million) or 4% of annual global revenue, whichever is greater. The GDPR also confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies, and obtain compensation for damages resulting from violations of the GDPR. The GDPR may increase our responsibility and liability in relation to personal data that we process where such processing is subject to the GDPR, and we may be required to put in place additional mechanisms to ensure compliance with the GDPR, including as implemented by individual countries. Compliance with the GDPR will be a rigorous and time-intensive process that may increase our cost of doing business or require us to change our business practices, and despite those efforts, there is a risk that we may be subject to fines and penalties, litigation, and reputational harm in connection with our European activities.

Significantly, adequate safeguards must be implemented to enable the transfer of personal data outside of the EEA or the UK, in particular to the United States, in compliance with the GDPR (for example, the European Commission approved Standard Contractual Clauses, or SCCs, and the UK International Data Transfer Agreement/Addendum ("UK IDTA"). Where relying on the SCCs /UK IDTA for data transfers, we may also be required to carry out transfer impact assessments to assess whether the recipient is subject to local laws which allow public authority access to personal data. The international transfer obligations under the EEA and UK data protection regimes will require significant effort and cost, and may result in us needing to make strategic considerations around where EEA and UK personal data is transferred and which service providers we can utilize for the processing of EEA and UK personal data.

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 and may not comply under one or more of such laws, regulations or guidance. 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 share 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, as well as additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, any of which could adversely affect our ability to operate our business and our financial results.

If we or our CDMOs and CROs 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 and third parties such as our CDMOs and CROs 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 partly in the United Kingdom and EU countries, 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 the United Kingdom and other 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 UK 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 or practice;

- 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, mis-classification 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, fires and public health epidemics and pandemics, including the current COVID-19 global pandemic.

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 patents and patent applications relating to the lentiviral vectors used in the manufacture or use of one or more our product candidates or relating to one or more 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 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.

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 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, including technology related to the manufacture and use of our products and product candidates. We have in-licensed certain know-how and data from GSK and Telethon-OSR relating to Libmeldy, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and pre-clinical programs. 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.

Our in-licensed intellectual property is often limited to particular fields and is often subject to certain retained rights. We may not have rights to use in-licensed intellectual property, data or know-how from one program in another program. 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 particular licensor may have the right to terminate such agreements. 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 Libmeldy. 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.

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 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. 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 may 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 they 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 we or one of our licensing partners 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.

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.

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 may have been generated through the use of U.S. government and 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.

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 they 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.

We may become involved in lawsuits to protect or enforce our patents and 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 future 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, a court may decide not to grant an injunction against the offender and instead award only monetary damages, which 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.

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.

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, which could impair 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.

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. 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 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 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.

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.

The trading price of our ADSs has fluctuated and may continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control. For example, the trading price of our ADSs may be affected by:

- adverse results or delays in pre-clinical 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 our current or future collaborators to successfully develop and commercialize product candidates for which we are eligible to receive milestone and royalty payments;
- failure by us to adequately scale our manufacturing capabilities and commercial and sales organization to succeed in our commercialization efforts of Libmeldy;
- failure by us to succeed in our ongoing commercialization of Strimvelis;
- failure by us to gain broad insurance coverage and reimbursement for our product candidates, if approved;
- 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 or other projections we may provide to the public;
- failure by us to meet or exceed the financial or other 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;
- general economic, geopolitical and market conditions, including the significant disruptions to the U.S. and global economies and the related significant volatility and negative pressure in financial markets caused by the COVID-19 global pandemic, supply chain issues, inflationary pressures and the ongoing conflict in the Ukraine;
- 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 the Nasdaq Capital Market and 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.

If securities or industry analysts do not continue to publish research about our business or publish inaccurate or unfavorable research, 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 March 3, 2023, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 47.6% of our ordinary shares and ADSs. In computing the number of ordinary shares beneficially owned by a person, ordinary shares subject to options, or other rights held by such person that are currently exercisable or will become exercisable within 60 days of March 3, 2023, are considered outstanding. These ordinary shares, however, are not included in the number of shares outstanding as of March 3, 2023. (In other words, in calculating the beneficial ownership percentage, there are ordinary shares in the numerator that are not reflected in the denominator.) Depending on the level of attendance at our 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 meeting. Any shareholder or group of shareholders controlling more than 50% of the share capital present and voting at our 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, and the approval of certain significant corporate transactions. 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 and have held their ordinary shares for a longer period, they may be more interested in selling our company to an acquirer than other investors or they may want us to pursue strategies that deviate from the interests of other shareholders.

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

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. Additionally, we filed a registration statement with the SEC and may issue securities in one or more underwritten transactions, in "at-the-market" offerings or in other transactions from time to time. If we were to issue such securities in the public market, the trading price of our ADSs could decline.

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. If the terms of an amendment are materially disadvantageous to ADS holders, ADS holders are only entitled to receive 30 days' advance notice of the amendment and no prior consent of the ADS holders is required. Furthermore, we may decide to direct the depositary to terminate the ADS facility at any time for any reason. For example, termination may occur if 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 if we become the subject of a takeover or a going-private transaction. If the ADS facility terminates, ADS holders will receive at least 30 days' prior notice but no prior consent is required from them. If we 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 they 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 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 or the depositary. If a lawsuit is brought against us 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 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.

Sales of a substantial number of our ADSs in the public market by our existing shareholders could cause the market price of our ADSs to drop significantly.

Sales of a substantial number of our ADS in the public market, or the perception that holders of a large number of ADSs intend to sell, could reduce the market price of our ADSs. As of December 31, 2022, we had outstanding 126,947,225 voting shares. The holders of 8,611,375 shares of our ordinary shares are entitled to rights with respect to the registration of their ordinary shares under the Securities Act of 1933, as amended, or the Securities Act. Registration of these ordinary shares under the Securities Act would result in the ADSs representing them becoming freely tradable without restriction, except for ADSs purchased by affiliates. In addition, our directors, executive officers and other affiliates may establish, and certain executive officers, directors and affiliates have established, programmatic selling plans under Rule 10b5-1 of the Exchange Act, for the purpose of effecting sales of our ADSs. Generally, sales under such plans by our executive officers and directors require public filings. Any sales of securities by these shareholders, or the perception that those sales may occur, under such programmed selling plans, could have a material adverse effect on the trading price of our ADSs. In addition, as of December 31, 2022, 18,488,043 ordinary shares reserved for issuance upon the exercise of existing options outstanding and issuance of performance-based and time-based restricted shares 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.

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 public company listed on a U.S. Exchange, 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 of the Sarbanes-Oxley Act, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting and, once we are no longer a "smaller reporting company", we will be required to furnish an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. In order to achieve and maintain compliance with Section 404, we have documented and evaluated 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 continually 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 in any given year that we will not be able to conclude within the prescribed time frame 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. Moreover, if in the future we are required to obtain an opinion as to the effectiveness of our internal control over financial reporting and if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our ADSs could be negatively affected, and we could become subject to investigations by the SEC or other regulatory authorities or to shareholder litigation, which could have an adverse impact on the market price or our ADSs and cause us to incur additional expenses.

Shareholder protections and restrictions found in provisions under The City Code on Takeovers and Mergers do not apply to us.

In February 2020, the UK Takeover Panel confirmed that we are not considered to be subject to The City Code on Takeovers and Mergers, or The Takeover Code, and, as a result, our shareholders are not 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 and which may operate to prohibit certain arrangements and courses of conduct considered customary in the United States. There are no provisions in our Articles of Association that replicate the provisions of The Takeover Code.

We believe that this position is unlikely to change at any time in the near future, but in accordance with good practice, we will review the situation on a regular basis and cooperate and consult with the UK Takeover Panel if there is any material change in our circumstances with respect to matters which the UK Takeover Panel might consider relevant in their determination of jurisdiction over us.

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 UK 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 certain significant transactions.
- In the United Kingdom, takeovers may be structured as takeover offers or as schemes of arrangement. Under English law, 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.

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, testing required to be conducted by us in connection with Section 404, and 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.

We are required to disclose changes made in our internal controls and procedures on a quarterly basis, and our management is required to assess the effectiveness of these controls annually. However, for as long as we are a "smaller reporting company," our independent registered public accounting firm will not be required to attest to the effectiveness of our internal control

over financial reporting pursuant to Section 404. We will qualify as a "smaller reporting company" if the market value of our ADSs held by non-affiliates is below $250 million (or $700 million if our annual revenue is less than $100 million) as of the last business day of our most recently completed second fiscal quarter. An independent assessment of the effectiveness of our internal control over financial reporting could detect problems that our management's assessment might not. Undetected material weaknesses in our internal control over financial reporting could lead to financial statement restatements and require us to incur the expense of remediation.

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.

We are not currently in compliance with the minimum bid price rule of the Nasdaq Capital Market, and a delisting could limit the liquidity of our ADSs, increase their volatility and hinder our ability to raise capital.

We are not currently in compliance with The Nasdaq Stock Market's minimum bid price rule because the closing bid price of our ADSs had been below $1.00 per share for 30 consecutive business days. On March 10, 2023, we effected a change to our ADS to ordinary share ratio from the previous ratio of one ADS to one ordinary share to a new ratio of one ADS to ten ordinary shares. We expect that we will regain compliance with the minimum bid price rule as a result of the ratio change. However, we may not be able to remain compliant in the future.

If we are not able to maintain compliance with the Nasdaq listing requirements, including the minimum bid price rule, we could receive a delisting notice from Nasdaq. Delisting from The Nasdaq Capital Market could make trading our ADSs more difficult for investors, potentially leading to declines in the trading price of our ADSs and decreased liquidity. We cannot ensure that our ADSs, if delisted from the Nasdaq Capital Market, will be listed on another national securities exchange or quoted on an over-the-counter system. Other consequences of delisting could include an adverse effect on our ability to obtain equity financing on acceptable terms or at all, an increase in volatility of our ADS trading price, and a loss of confidence by shareholders, employees and business partners.

Risks related to taxation

Changes in tax law could adversely affect our business and financial condition.

We conduct business globally. The tax treatment of the company or any of the group companies could be materially adversely affected by several factors, including, but not limited to: (i) changing tax laws, regulations and treaties, or the interpretation thereof; (ii) tax policy initiatives and reforms under consideration (such as those related to the Organization for Economic Co-Operation and Development's, or OECD, Base Erosion and Profit Shifting, or BEPS, Project, the European Commission's state aid investigations and other initiatives); (iii) the practices of tax authorities in jurisdictions in which we operate; and (iv) the resolution of issues arising from tax audits or examinations and any related interest or penalties. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid.

We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, but such changes, to the extent they are brought into tax legislation, regulations, policies or practices in jurisdictions in which we operate, could affect our financial position, future results of operations, cash flows in a particular period and overall or effective tax rates in the future in countries where we have operations, reduce post-tax returns to our shareholders and increase the complexity, burden and cost of tax compliance.

Taxing authorities could challenge our historical and future tax positions or our allocation of taxable income among our subsidiaries, and tax laws to which we are subject could change in a manner adverse to us.

We operate through various subsidiaries in a number of countries throughout the world. Consequently, we are subject to tax laws, treaties, and regulations in the countries in which we operate, and these laws and treaties are subject to interpretation. We have taken, and will continue to take, tax positions based on our interpretation of such tax laws.

Our transfer pricing arrangements are not generally binding on applicable tax authorities. The price charged for products, services, or the royalty rates and other amounts paid for intellectual property rights, could be challenged by the various tax authorities, resulting in additional tax liability, interest or penalties. There can be no assurance that a taxing authority will not have a different interpretation of applicable law and assess us with additional taxes. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a ''permanent establishment'' under international tax treaties, and such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. If we are assessed with additional taxes, this may result in a material adverse effect on our results of operations and financial condition.

A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, for example where there has been a technical violation of contradictory laws and regulations that are relatively new and have not been subject to extensive review or interpretation, in which case we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable, or result in other liabilities.

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 2022 taxable year, but 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 (i) 75% or more of our gross income consists of passive income or (ii) 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 ordinary shares or ADSs, 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.

Based on the current and expected composition of our income and assets and the value of our assets, we believe that we were a PFIC for U.S. federal income tax purposes for our taxable year ended December 31, 2022. 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. Because it was possible we were a PFIC for the 2022 taxable year, we currently expect that we will provide the information necessary for U.S. holders to make a QEF Election. We may elect to provide such information on our website (www.ORTX.com). A U.S. holder would also 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 UK net operating loss and tax credit carryforwards and certain built-in losses to reduce future tax payments or benefit from favorable UK tax legislation.

As a UK incorporated and tax resident entity, we are subject to UK 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 UK corporation tax. As of December 31, 2022, we had cumulative carryforward tax losses of $633.4 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to UK profits incurred on or after April 1, 2017 will be limited each year to £5.0 million plus, broadly, an incremental 50% of UK 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 two UK 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 Credit 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 currently eligible for inclusion within these tax credit cash rebate claims.

In the future we will continue to seek to benefit from these programs; however, the United Kingdom Government's Autumn Statement on November 17, 2022 announced reductions in the level of credits offered under the SME Program that will take effect from April 2023, along with other changes outlined further below. Under the SME Program, we are currently in principle able to surrender some of our trading losses that arise from our qualifying research and development activities for a cash rebate of up to 33.35% of such qualifying research and development expenditures. The majority of our research, clinical trials management and manufacturing development activities are currently eligible for inclusion within these tax credit cash rebate claims. The cash rebate available from April 2023 is expected to reduce to up to 18.6% of qualifying research and development expenditures, which (if we continue to qualify as a SME) would represent a significant reduction in cash receivable from the United Kingdom Government. Furthermore, we may not be able to continue to claim payable research and development tax credits in the future if we cease to qualify as a SME, based on size criteria concerning employee headcount, turnover and gross assets. There is also a cap on payable credit claims under the SME Program in excess of £20,000 by reference to, broadly, three times the total PAYE and NICs liability of the company, subject to an exception which prevents the cap from applying. That exception requires the company to be creating, taking steps to create or managing intellectual property, as well as having qualifying research and development expenditure in respect of connected parties which does not exceed 15% of the total claimed. If such exception does not apply, this could restrict the amount of payable credit that we claim. If we cease to be eligible for the SME Program, we may be able to claim alternative credits under the RDEC Program (in addition to credits that we currently claim under that Program). The RDEC Program does not entitle us to cash rebates in the same way as the SME Program, but instead (broadly) functions as a taxable credit against United Kingdom corporation tax (although the credit may be repayable to a loss-making company in certain circumstances). The United Kingdom Government has announced an increase to the rate of the RDEC credit from 13% to 20% from April 2023 (although the RDEC Program on the whole is less advantageous than the SME Program).

Additional changes to the R&D tax relief legislation, expected to take effect from April 2023, introduce restrictions on relief that may be claimed for expenditure on sub-contracted R&D activity, broadly requiring either that workers carrying on such activity are subject to UK PAYE or, where work is undertaken outside the UK, that this must be due to geographical, environmental or social conditions not replicable in the UK. These restrictions may impact the quantum of R&D relief that we are able to claim in the future. In addition, the UK government is currently consulting on the potential replacement of the SME Program and RDEC Program with a single program, operating similarly to the RDEC Program, which may, inter alia,

change the present treatment of sub-contracted R&D work and introduce different thresholds and caps on expenditure and relief. If enacted, the new program would be expected to have effect for expenditure incurred from April 2024 onward, and could have a material impact on the quantum of R&D relief that we are eligible to claim.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenue 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 revenue 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 UK 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.

Our ability to use our U.S. tax attributes may be limited.

Under Section 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if a corporation undergoes an "ownership change," generally defined as a greater than 50% change (by value) in its equity ownership by certain stockholders over a three-year period, the corporation's ability to use its pre-change tax attributes (such as research and development tax credits) to offset its post-change tax liabilities may be limited. We have completed several financings since our inception, which we believe have resulted in an ownership change as defined by Section 382 of the Code. We may also experience ownership changes in the future as a result of subsequent shifts in our share ownership. As a result, if we incur U.S. federal tax liability, our ability to use our pre-change tax attributes to offset U.S. federal tax liability may be subject to limitations, which could potentially result in increased future tax liability to us.

Risks related to our Domicile

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 headquartered in the United Kingdom, we also 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.

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 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 persons 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.

General Risk Factors

We have debt service obligations and may incur additional indebtedness in the future, which could adversely affect our financial condition, our results of operations and our ability to react to changes in our business.

We currently have $32.2 million of principal indebtedness outstanding under our senior term facilities agreement, or the amended Credit Facility, with MidCap Financial (Ireland) Limited. We have the ability to borrow up to an additional $67.0 million in the future under the Amended Credit Facility upon satisfaction of certain conditions. Our existing indebtedness and any additional indebtedness we may incur could require us to divert funds identified for other purposes for debt service and impair our liquidity position.

The fact that a portion of our cash, cash equivalents and marketable securities could be required to make payments on our indebtedness could have important consequences, including:

- increasing our vulnerability to general adverse economic and industry conditions or increased interest rates;
- restricting our ability to use our cash, cash equivalents and marketable securities for other purposes;
- limiting our flexibility in planning for or reacting to changes in our business and the markets in which we operate, which would place us at a competitive disadvantage compared to our competitors that may have less debt;
- limiting our ability to borrow additional funds for working capital, capital expenditures and other investments; and
- failing to comply with the covenants in our debt agreements could result in all of our indebtedness becoming immediately due and payable.

If our business does not generate sufficient cash flow from operations or if future borrowings are not available to us under the Amended Credit Facility or otherwise in amounts sufficient to enable us to fund our liquidity needs, our financial condition and results of operations may be adversely affected. Our inability to make scheduled payments on our debt obligations in the future would require us to refinance all or a portion of our indebtedness on or before maturity, sell assets or seek additional equity investment. We may not be able to take any of such actions on a timely basis on terms satisfactory to us or at all.

The Amended Credit Facility contains customary restrictive covenants relating to the operation of our business, including restrictions on our ability to:

- incur or guarantee additional indebtedness;
- incur or permit to exist certain liens;
- undergo a change in control;
- amend material agreements and organizational documents;
- effect certain mergers, consolidations, asset sales and acquisitions; and
- pay dividends on, or redeem or repurchase, share capital, enter into transactions with affiliates, or materially change our business.

Such restrictions could affect our ability to take certain actions from time to time.

We may be adversely affected by natural disasters, and our business continuity and disaster recovery plans may not adequately protect us.

Natural disasters, including earthquakes, fires, flooding, and health epidemics and pandemics, among other things, could severely disrupt our business. If a natural disaster occurred, we may be unable to use all or a significant portion of our facilities, which could make it difficult or impossible for us to continue our business or a portion of our business for a substantial period of time. A natural disaster could also damage critical infrastructure and affect our third-party contract manufacturers. Our disaster recovery and business continuity plans are currently limited and may not prove adequate in the event of a serious natural disaster or similar event. As such, we could incur substantial expenses if a natural disaster occurs, which could have a material impact on our business.

Our business may be affected by public health crises, including the COVID-19 pandemic.

Public health crises such as pandemics or similar outbreaks can adversely impact our business. For example, the COVID-19 global pandemic caused significant disruptions to the U.S. and global economies, contributed to volatility in the financial markets, and led to measures that impacted various aspects of our business, including our clinical and regulatory efforts as well as our supply chain. Renewed outbreaks, including different variants of the virus, could negatively impact our business operations.

In addition, in response to the COVID-19 pandemic, we implemented a hybrid work policy for many employees, whereby eligible employees spend only part of their time working in the office. Remote working creates risks to our business, including increased cybersecurity risks. We may also experience difficulty in recruiting and onboarding new employees as a result of remote working.

The extent to which pandemics, including the COVID-19 pandemic, may impact our business, and our clinical development and regulatory efforts, as well as our supply chain, will depend on future developments that are highly uncertain and cannot be predicted with confidence, such as the geographic spread of a disease, the duration of the outbreak, government actions, such as travel restrictions, quarantines and social distancing requirements in the U.S. and in other countries, business closures or business disruptions and the effectiveness of actions taken in the U.S. and in other countries to contain and treat the disease. Accordingly, we cannot predict the impact of pandemics, including the COVID-19 pandemic, with any certainty. However, these effects could materially and adversely affect our business, financial condition, results of operations and growth prospects, which may in turn also have the effect of heightening many of the other risks and uncertainties described elsewhere in this "Risk Factors" section.

Any changes to existing accounting pronouncements or taxation rules or practices may cause adverse fluctuations in our reported results of operations or affect how we conduct our business.

A change in accounting pronouncements or taxation rules or practices could have a significant effect on our reported results and may affect our reporting of transactions completed before the change is effective. New accounting pronouncements, taxation rules and varying interpretations of accounting pronouncements or taxation rules have occurred in the past and may occur in the future. We could be required to modify a current tax or accounting position as a result of any such change, and this could adversely affect our reported financial results and could change the way we conduct our business.

We could be subject to securities class action litigation.

We could be the subject of a securities class action litigation. The risk is especially relevant to us because such litigation is often brought against companies following a decline in the market price of their securities, and biotechnology and pharmaceutical companies have experienced significant securities price volatility in recent years. If such a litigation were brought against us, it could result in substantial costs and could divert management's attention and resources, which would be harmful to our business.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Facilities

Our principal office is located at 245 Hammersmith Road, 3rd Floor, London W6 8PW, United Kingdom. We lease approximately 17,400 square feet of office space at this location and our lease for this location extends through February 2032. We also lease approximately 14,000 square feet of office space in Boston, Massachusetts, our U.S. Headquarters.

In December 2018, we entered into an agreement to lease approximately 153,000 square feet of manufacturing and office space in Fremont, California. This lease extends through May 2030. We have abandoned plans to build-out the facility and have subleased the facility to a third-party for the remainder of the lease term.

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

Item 3. 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. As of December 31, 2022, we were not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information and Holders of Ordinary Shares and ADSs

Prior to March 10, 2023, our American Depositary Shares, or ADSs, each represented one ordinary share, nominal value £0.10 per share, of Orchard Therapeutics plc. On March 10, 2023, we effected a change to our ADS to ordinary share ratio such that one ADS is now represented by ten ordinary shares. An ADS may be evidenced by an American Depositary Receipt issued by Citibank, N.A. as depositary bank. Our ADSs have been listed and traded on The Nasdaq Capital Market since September 13, 2022 and were previously listed and traded on The Nasdaq Global Select Market since October 31, 2018. Our ADSs are listed and trade under the symbol "ORTX". As of March 10, 2023, there were 55 holders of record of our ordinary shares and one holder of record of our ADSs.

The closing sale price of our ADS on March 10, 2023 was $4.80, which reflects the above-mentioned ratio change.

Sales of Unregistered Securities

Not applicable.

Dividends

Since our inception, we have not declared or paid any dividends on our ordinary shares. We intend to retain any earnings for use in our business and do not currently intend to pay dividends on our ordinary shares.

The payment of dividends by us is governed by English law. The declaration and payment of any future dividends will be at the discretion of our board of directors and will depend upon our results of operations, cash requirements, financial condition, contractual restrictions, restrictions imposed by our indebtedness, any future debt agreements or applicable laws and other factors that our board of directors may deem relevant.

Information about Our Equity Compensation Plans

Information regarding our equity compensation plans is incorporated by reference in Item 12 of Part III of this Annual Report.

Item 6. Reserved.

Not applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion of our financial condition and results of operations should be read in conjunction with our consolidated financial statements and related notes included elsewhere in this report. Some of the information contained in this discussion and analysis and set forth elsewhere in this report, including information with respect to our plans and strategy for our business, includes forward-looking statements that involve risks and uncertainties. You should review the section titled "Risk Factors" in Part I—Item 1A of this report for a discussion of important factors that could cause actual results to differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis.

Business Overview

Orchard Therapeutics is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. Our *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach harnesses the power of genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. We have one of the most advanced gene therapy pipelines in the industry spanning multiple therapeutic areas where the disease burden on children, families and caregivers is immense and current treatment options are limited or do not exist.

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, commercializing Libmeldy in Europe, 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 equity securities, including American Depositary Shares ("ADSs") in our initial public offering ("IPO") and follow-on offering, ordinary shares in our private placement, and convertible preferred shares. We have also financed our operations through proceeds from our senior term facilities agreement (the "Amended Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., and proceeds associated two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program.

We have incurred significant operating losses since our inception. With the approval of Libmeldy in Europe, we are now transitioning from a primarily clinical development stage company to a commercial stage company. We plan to continue the implementation of our commercialization plan for Libmeldy and our near-term plans for commercialization include:

- Enabling patient identification via multi-pronged diagnostics initiatives and newborn screening in Europe and the U.S.;
- Expanding global footprint by qualifying leading centers with transplant and disease area expertise;
- Leveraging cross-border and treatment abroad reimbursement pathways in Europe, Middle East, and Turkey;
- Securing market access via multi-stakeholder engagement with various payment models.

Our net losses were $150.7 million for the year ended December 31, 2022. As of December 31, 2022, we had an accumulated deficit of $900.9 million. As of December 31, 2022, we had cash, cash equivalents and marketable securities of $143.8 million. Our 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.

Recent Developments

In March 2022, we announced our decision to focus on severe neurometabolic diseases and early research programs, and to discontinue our investment in and seek strategic alternatives for our programs in rare primary immune deficiencies, including OTL-103 for treatment of WAS, OTL-102 for treatment of X-CGD and Strimvelis. In connection with this new strategic focus, we reduced our workforce by approximately 30%.

In March 2023, the Company announced a private placement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares, and warrants to purchase ordinary shares or non-voting ordinary shares. The private placement consists of two closings. The Company completed the initial closing in March 2023 and sold 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share, and warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per ten shares and accompanying warrant. The completion of the initial closing resulted in gross proceeds of approximately $34.0 million. Refer to the Liquidity section below for further information on the private placement.

Business update regarding COVID-19

The COVID-19 pandemic presented substantial public health and economic challenges around the world, and it will likely continue to affect our business. In addition to general macro-economic effects of the pandemic, our business faced several specific challenges. For example, many of our clinical sites devoted, and continue to devote, significant resources to patients with COVID-19. If there is a future rise in hospitalizations, our clinical sites may need to dedicate additional resources to treating these people, which could limit their ability to enroll additional patients in clinical trials, if necessary.

In addition, during the pandemic, many of our employees spent time working from home due to limitations on travel and other social distancing measures. Currently, a majority of employees are on a hybrid-working model, meaning they perform part of their work in the office and part of their work outside of the office. This could increase our cybersecurity risk and hinder our ability to onboard new employees.

It is possible that if additional variants of the virus proliferate, our third party vendors and contract manufacturers could face delays and may struggle to operate at expected levels. While we don't currently anticipate any interruptions to our business, we cannot predict this.

Finally, if there are future disruptions to the capital markets as a result of the pandemic, it could impact our ability to raise capital.

For additional information on the various risks posed by the COVID-19 pandemic, please see the section titled "Item 1A. Risk Factors" included in this Annual Report.

Components of our results of operations

Product revenue

We recognize product revenue, net, from sales of Libmeldy and Strimvelis in Europe. Product revenue is recorded net of estimates of variable consideration. Please read Note 2, Product revenue, net, to the consolidated financial statements included in this Form 10-K for further details of the reserves recorded for variable consideration. We expect that future sales of Libmeldy will fluctuate quarter over quarter. Strimvelis is distributed exclusively at the San Raffaele Hospital in Milan, Italy. We announced in March 2022 that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

We recognize collaboration revenue under our collaboration agreement with Pharming. Under revenue recognition guidance, we account for our obligations to provide the license and research, development, and manufacturing services under the agreement as a series of distinct services that are accounted for as a single performance obligation. We recognize revenue using the cost-to-cost input method, which we believe best depicts the transfer of control to the customer. Under the cost-to-cost input method, the extent of progress towards completion is measured based on the ratio of actual costs incurred to the total estimated costs expected upon satisfying the identified performance obligation. Revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. The impact of any adjustment related to the estimated transaction price on revenue recorded to date is recognized in the period the adjustment is identified. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred. Refer to Note 2 and Note 16 to the consolidated financial statements included in this Form 10-K for further discussion on our revenue recognition around this agreement.

Cost of product revenue

Cost of sales consists of costs to manufacture, including raw materials, distribute and administer Libmeldy and Strimvelis and royalty payments due to third parties that are tied to sales.

A portion of our inventory includes raw materials that were expensed prior to approval of Libmeldy, referred to as zero cost inventories. Cost of sales for newly launched products will not include the full cost of manufacturing until the initial pre-launch inventory is depleted, and additional inventory is purchased, manufactured, and sold. Therefore, the cost of product revenue reflects a portion but not all of the manufacturing costs of our products.

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 contract research organizations (CROs) that conduct research, pre-clinical activities and clinical trials on our behalf as well as contract manufacturing organizations that manufacture lentiviral vectors and cell-based drug products for use in our pre-clinical 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 related to research and development performed associated with the Company's collaboration arrangement;
- costs of outside consultants, including their fees, share-based compensation and related travel expenses;
- the costs of laboratory supplies and acquiring, developing and manufacturing pre-clinical 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, costs related to our collaboration agreements, and other operating costs;
- upfront, milestone and management fees for maintaining licenses under our third-party licensing agreements; and
- grant awards or other government incentives unrelated to income taxes that we earn that are recorded as an offset to the related research and development costs incurred.

We expense research and development costs 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 prepaid expenses or accrued research and development expenses. United Kingdom research and development tax credits are recorded as an offset to research and development expense. Amortization of the Strimvelis loss provision is also recorded as an offset to research and development expense.

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 contract manufacturing organizations in connection with our pre-clinical 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 for development are included in unallocated costs. We do not allocate employee costs, costs associated with our early-stage 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 or the manufacturing requirements to conduct those clinical trials. We expect that our research and development expenses will continue to decline due to the portfolio updates and workforce reduction we undertook in 2022 as well as the completion of certain activities to support an OTL-200 BLA submission.

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.

Other income (expense), net

Interest income

Interest income consists of income earned on our cash and cash equivalents and marketable securities.

Interest expense

Interest expense consists of interest associated with our credit facility with MidCap Financial, which we entered into in May 2019 and amended and restated in May 2021. During 2022, this credit facility bore a variable interest rate of 5.95% above LIBOR, plus a final payment equal to 3.5% of the principal borrowed under the credit facility.

In January 2023, we again amended and restated the credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

Other income (expense)

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

Results of operations

Comparison of the years ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Product revenue, net	$ 20,610	$ 700	$ 19,910
Collaboration revenue	2,045	975	1,070
Total revenues	$ 22,655	$ 1,675	$ 20,980
Costs and operating expenses			
Cost of product revenue	6,771	226	6,545
Research and development	93,847	86,977	6,870
Selling, general and administrative	49,125	54,905	(5,780)
Total costs and operating expenses	149,743	142,108	7,635
Loss from operations	(127,088)	(140,433)	13,345
Other (expense) income:			
Interest income	1,543	412	1,131
Interest expense	(3,079)	(2,497)	(582)
Other (expense) income, net	(24,410)	(1,238)	(23,172)
Total other (expense) income, net	(25,946)	(3,323)	(22,623)
Net loss before income tax	(153,034)	(143,756)	(9,278)
Income tax (expense) benefit	2,374	(828)	3,202
Net loss attributable to ordinary shareholders	$ (150,660)	$ (144,584)	$ (6,076)

Product revenue, net

The table below summarizes our revenue earned by product (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Libmeldy	$ 18,796	$ —	$ 18,796
Strimvelis	1,814	700	1,114
Total product revenue, net	$ 20,610	$ 700	$ 19,910

Libmeldy received approval from the European Commission in December 2020 and we made our first commercial sale in the first quarter of 2022. In March 2022, we announced that we would discontinue our investment in and seek alternatives for Strimvelis.

Collaboration revenue

During the years ended December 31, 2022 and 2021, we recognized revenue of $2.0 million and $1.0 million, respectively, under our collaboration agreement with Pharming. We recognize revenue using the cost-to-cost input method. Under this method, revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred.

Cost of product revenue

Cost of product revenue for the year ended December 31, 2022, consisted of costs to manufacture, distribute and administer Libmeldy and Strimvelis and royalty payments due to third parties related to these sales. The gross margin on our product revenue, net was enhanced by our use of zero cost inventories. Utilizing the per unit average cost of materials that were purchased prior to approval and expensed that were utilized in the manufacturing process for our products sold during the period, cost of product revenue for the year ended December 31, 2022, would have been approximately $8.4 million.

Research and development expenses

The table below summarizes our research and development expenses by therapeutic area (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	$ 28,813	$ 22,443	6,370
Primary immune deficiencies	9,777	17,801	(8,024)
Blood disorders	3,041	743	2,298
Other research and pre-clinical programs under development	3,927	5,636	(1,709)
Total direct research and development expenses	45,558	46,623	(1,065)
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	31,108	31,897	(789)
Share-based compensation	6,791	9,214	(2,423)
Restructuring costs	1,448	524	924
Accretion of Strimvelis loss provision	(274)	(1,037)	763
Research and development tax credit	(8,243)	(13,920)	5,677
Facility and other	17,459	13,676	3,783
Total indirect research and development expenses	48,289	40,354	7,935
Total research and development expenses	$ 93,847	$ 86,977	6,870

Total direct research and development expenses decreased from $46.6 million for the year ended December 31, 2021, to $45.5 million for the year ended December 31, 2022. The $1.1 million decrease, or -2%, was primarily the result of:

- an $8.0 million decrease in costs associated with primary immune deficiencies programs and a $1.7 million decrease in other research and pre-clinical programs due to due to de-prioritization of and decreased investment in these programs after our restructuring efforts;
- a $6.4 million increase in spending on neurometabolic disorder programs, specifically driven by spending on OTL-200 for MLD, as we ramp up our efforts to file a BLA with the FDA; and
- a $2.3 million increase in spending on blood disorder program which was driven by the accruing of long-term follow up cost associated with returning the program to the licensee and other wind-down costs related to de-prioritization of the program after our restructuring efforts.

Total indirect research and development expenses increased from $40.4 million for the year ended December 31, 2021, to $48.3 million for the year ended December 31, 2022. The $7.9 million increase, or 20%, was the result of:

- a $5.7 million decrease in the amount received from the UK research and development tax credit, which is an offset to research and development expenses incurred for qualifying programs. This decrease was driven by a decrease in qualifying costs;
- a $3.8 million increase in facility and other expenses due to increases in platform development costs;
- a $0.9 million increase in restructuring costs driven by re-prioritization of our goals and changes in our corporate strategy and associated employee terminations;
- a $0.8 million decrease in the accretion of the Strimvelis loss provision, which is an offset to research and development expenses. This decrease was driven by our decision to no longer invest in the development of our commercial program for Strimvelis and seek an alternative future for the program; and
- a $2.4 million decrease in share-based compensation and a $0.8 million decrease in personnel related costs due to our strategic restructuring efforts and headcount reduction.

Selling, general and administrative expenses

The table below summarizes our selling, general and administrative expenses by functional area (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	$ 16,868	$ 18,227	(1,359)
Share-based compensation	9,219	13,322	(4,103)
Restructuring costs	333	484	(151)
Consulting, professional, and insurance-related costs	11,754	12,679	(925)
Marketing, promotions, and advocacy	4,135	5,259	(1,124)
Facilities and other costs	6,816	4,934	1,882
Total selling, general, and administrative expenses:	$ 49,125	$ 54,905	$ (5,780)

Selling, general and administrative expenses decreased from $54.9 million for the year ended December 31, 2021, to $49.1 million for the year ended December 31, 2022. The $5.8 million decrease, or -11%, was a result of:

- a $1.4 million decrease in personnel related expenses and a $4.1 million decrease in share-based compensation expenses due to decreased headcount as a result of our strategic restructuring;
- a $0.9 million decrease in consulting, professional, and insurance-related costs as well as a $1.1 million decrease in marketing, promotions, and advocacy costs due to a de-emphasis and discontinuation of investment in certain clinical and research programs as a result of our strategic restructuring; and
- a $1.9 million increase in facilities and other costs driven by increased shareholder and ADS administration costs.

Other (expense) income, net

Other (expense) income, net decreased from a $3.3 million loss for the year ended December 31, 2021, to a $25.9 million loss for the year ended December 31, 2022. During the year ended December 31, 2022, we had net realized and unrealized losses on foreign currency transactions of $24.4 million, comprised primarily of unrealized losses, compared to net realized and unrealized losses of $1.2 million for year ended December 31, 2021. Unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar, Pounds sterling, and Euro exchange rates. Interest expense was $3.1 million and $2.5 million for the years ended December 31, 2022 and 2021, respectively. Interest income was $1.5 million and $0.4 million in the years ended December 31, 2022 and 2021, respectively. The increase to both interest expense and interest income is attributable to interest rate increases throughout 2022 driven by anti-inflationary measures born from the current economic environment.

Liquidity and capital resources

From our inception through December 31, 2022, we have not generated significant revenue from product sales and incurred significant operating losses and negative cash flows from our operations. We acquired our commercial product Strimvelis and the program that is now Libmeldy from GSK in April 2018, and our product candidates are in various phases of pre-clinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We launched Libmeldy in Europe and generated product revenue during the year ended December 31, 2022. To date, we have financed our operations primarily with proceeds from the sale of ADSs in our IPO and follow-on offering, proceeds from the sale of ordinary shares in our private placement, proceeds from the sale of convertible preferred shares, reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure ("RDEC") program, 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 the California Institute of Regenerative Medicine ("CIRM"), upfront payments from our collaboration agreement with Pharming Group N.V., our Original Credit Facility and our Amended Credit Facility with MidCap, and through proceeds from sales of Libmeldy in Europe beginning in 2022.

On February 27, 2020, we entered into a Sales Agreement with Cowen and Company, LLC ("Cowen"), as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $100.0 million. On March 24, 2022, we delivered written notice to Cowen to terminate the Sales Agreement, effective as of March 30, 2022, pursuant to Section 11(b) thereof. Prior to termination, we had not sold any ADSs pursuant to the Sales Agreement. As a result of the termination of the Sales Agreement, we will not offer or sell any ADSs under the Sales Agreement. On October 6, 2022 we entered into a Sales Agreement with Guggenheim Securities, LLC, as agent, relating to an "at the market offering," pursuant to which we may issue and sell ADSs representing our ordinary shares, having an aggregate offering price of up to $30.0 million. As of December 31, 2022, we have not sold any shares under the Guggenheim Sales Agreement.

On March 6, 2023, we announced a private placement pursuant to which the Company agreed to sell up to an aggregate of 99,166,900 ordinary shares and non-voting ordinary shares, nominal value of £0.10 per share, and warrants to purchase an aggregate of 109,083,590 ordinary shares or non-voting ordinary shares. The private placement consists of two closings. At each closing, the shares will be sold in fixed combinations with the warrants and units, with each purchaser receiving one warrant to purchase eleven shares per ten shares purchased. The Company received approximately $34 million at the initial closing on March 10, 2023. The Company may receive an additional $34 million from the second closing of the private placement. This second closing is conditioned upon (i) the Company's announcement of its intention to file a biologics license application ("BLA") submission following receipt of the minutes from the U.S. Food and Drug Administration ("FDA") in connection with the Company's pre-BLA (Type B) meeting for OTL-200, provided such minutes do not expressly advise the Company not to proceed with a BLA submission, and (ii) receipt of approval from the Company's shareholders, to be provided at a meeting of shareholders no later than 120 days after the initial closing, to give the Company's directors authority to issue the securities to be issued and sold in the second closing of the private placement and the shares issuable upon exercise of the warrants to be issued and sold in the private placement.

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, lease, and debt obligations described below in the footnotes to our consolidated financial statements.

Cash flows

The following table summarizes our cash flows for each of the periods presented (in thousands):

	For the Year Ended December 31,	
	2022	2021
Net cash used in operating activities	$ (75,987)	$ (125,097)
Net cash provided by (used in) investing activities	90,560	(32,165)
Net cash provided by (used in) financing activities	(693)	158,066
Effect of exchange rate changes on cash	(1,419)	(27)
Net increase in cash, cash equivalents, and restricted cash	$ 12,461	$ 777

Operating activities

Net cash used in operating activities for the year ended December 31, 2022, was $76.0 million and was primarily driven by our net loss of $150.7 million, partially offset by non-cash charges consisting of depreciation and amortization of $2.7 million, share based compensation of $16.0 million, and unrealized foreign currency transaction losses on intercompany

accounts of $23.2 million. Our net cash used in operating activities also included a net source of cash of $36.2 million related to changes in operating assets and liabilities as follows:

- a net source of cash of $22.6 million related to the receipt of funds from our UK research and development tax credit for claims submitted for the year ended December 31, 2021;
- a net source of cash of $13.6 million related to changes in accounts payable, accrued expenses, and other current liabilities primarily driven to timing of invoices as compared to when services are provided by our vendors as well as the accrual of remaining costs for discontinued clinical and research expenses for which we have discontinued further investment due to our corporate restructuring activities;
- a net source of cash of $2.2 million related to increased other long-term liabilities due to timing of payments of certain accrued royalties;
- a net source of cash of $5.1 million from a decrease in prepaid expenses, other current assets, and other assets primarily due to services being performed on amounts already paid to vendors; and
- a net use of cash of $7.4 million related increased accounts receivable due to timing of cash receipt on our revenues.

During 2021, operating activities used $125.1 million of cash, primarily resulting from our net loss of $144.6 million. Cash usage from changes in our operating assets and liabilities was $17.1 million. There was cash usage of $13.9 million from our UK research and development tax credit receivable, consisting of claims that were filed in December 2021 that we expect to receive in 2022. Further, payment of accruals and accounts payable resulted in cash outflows of $9.5 million. These were offset by a $13.1 million increase in deferred revenue associated with our strategic collaboration with Pharming. Non-cash adjustments to operating activities of $36.6 million was primarily due to $22.5 million in non-cash share-based compensation expense, offset by $1.0 million in amortization of the Strimvelis loss provision as an offset to research and development expense. There were also unrealized foreign currency transaction losses on investments, intercompany accounts, and foreign-currency denominated payables and receivables held by our UK subsidiary of $9.7 million. Finally, we had $1.1 million in deferred income tax expense during 2021.

Investing activities

Net cash provided by investing activities for the year ended December 31, 2022, was $90.6 million. This net cash provided by investing activities was primarily driven by proceeds from the sales and maturities of marketable securities that we utilize for operating activities. We further received $8.0 million back from our Fremont lease construction deposit that was held in escrow and used $6.5 million to purchase property, plant, and equipment for our new Hammersmith office and lab space lease.

During 2021, we used $32.2 million of cash in investing activities. The change in cash from investing activity was primarily due to proceeds from sales and maturities of marketable debt securities that we utilize for operating activities.

Financing activities

Net cash used by financing activities for the year ended December 31, 2022, was $0.7 million and primarily consisted of repayments of the principal balance on our notes payable.

During 2021, we generated $158.1 million in cash from financing activities. This is primarily due to $143.6 million in proceeds from the issuance of ordinary shares in our private placement, after payment of $6.4 million in offering costs. We also generated $7.4 million associated with our entrance into the Amended Credit Facility. Further, we generated $4.1 million in proceeds associated with the Securities Purchase Agreement with Pharming that was entered into as part of our collaboration agreement. We generated $2.9 million in proceeds from the exercise of share options and issuance of ordinary shares as part of our ESPP.

Funding requirements

We expect our expenses and capital expenditures will remain consistent in the near term in connection with our ongoing activities as we advance the pre-clinical 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 Libmeldy in Europe, and for 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, and any other clinical trials that may be required to obtain marketing approval for our product candidates;
- perform research and development activities with respect to potential new product candidates;
- conduct investigational new drug application, or IND, and or clinical trial application, or CTA-enabling studies for our pre-clinical programs;
- initiate additional clinical trials and pre-clinical 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, to support technology and process innovations and to support manufacturing of product to commercial scale;
- develop and implement plans to establish and operate our own in-house manufacturing operations and facility;
- hire and retain additional personnel, such as non-clinical, clinical, pharmacovigilance, quality assurance, regulatory affairs, manufacturing, distribution, legal, compliance, medical affairs, finance, general and administrative, commercial and scientific personnel;
- develop, maintain, expand and protect our intellectual property portfolio; and
- 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 though we started generating Libmeldy product sales in 2022, 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, cash equivalents, and marketable securities on hand, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 private placement, will enable us to fund our operating expenses and capital expenditure requirements into 2025. 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.

United Kingdom research and development tax credit

As a company that carries out research and development activities, we are able to submit tax credit claims from two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure Credit ("RDEC") program depending on eligibility. 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.

Each reporting period, we evaluate which tax relief programs we are expected to be eligible for and record a reduction to research and development expense for the portion of the expense that we expect to qualify under the programs, that we plan to submit a claim for, and we have reasonable assurance that the amount will ultimately be realized. Based on criteria established by HM Revenue and Customs ("HMRC"), we expect a proportion of expenditures being carried in relation to our

pipeline research, clinical trials management and manufacturing development activities to be eligible for the research and development tax relief programs for the years ended December 31, 2022 and 2021.

The RDEC and SME credits are not dependent on us generating future taxable income or on our ongoing tax status or tax position. We have assessed our research and development activities and expenditures to determine whether the nature of the activities and expenditures will qualify for credit under the tax relief programs and whether the claims will ultimately be realized based on the allowable reimbursable expense criteria established by the UK government which are subject to interpretation. At each period end, we estimate the reimbursement available to us based on available information at the time.

We recognize credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expense. We make estimates of the research and development tax credit receivable as of each balance sheet date, based upon facts and circumstances known to us at the time. Although we do not expect our estimates to be materially different from amounts actually recognized, our estimates could differ from actual results. To date, there have not been any material adjustments to our prior estimates of the research and development tax credit receivable.

We may not be able to continue to claim research and development tax credits under the SME program in the future because it may no longer qualify as a small or medium-sized company. In addition, as noted above, the benefits offered by the SME program are to be reduced from April 2023 and may be subject to further reduction (or even withdrawal) in future, which could have a material impact on future credits that we may be eligible to claim, when compared to those we have benefited from in prior years. Furthermore, the UK government is currently consulting on the potential replacement of the R&D tax credit regime with a new regime, which may, inter alia, change the present treatment of sub-contracted R&D work and introduce different thresholds and caps on expenditure and relief. If enacted, the new program would be expected to have effect for expenditure incurred from April 2024 onward, and could have a material impact on the quantum of R&D relief and credits that we are eligible to claim.

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 prepaid and accrued expenses as of each balance sheet date in the consolidated financial statements based on facts and circumstances known to us at that time. 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.

We base our expenses related to pre-clinical studies and clinical trials on our estimates of the services received and efforts expended pursuant to quotes and contracts with multiple CROs, research institutions and other vendors that supply, conduct and manage pre-clinical 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 in the form of stock options with only service-based vesting conditions and record the expense for these awards using the straight-line method. We have also issued share-based awards with performance-based vesting conditions for which the expense is recognized when achievement of such performance conditions becomes probable.

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.

Product revenue, net - Libmeldy

In January 2022, we began generating product revenue from sales of Libmeldy in Europe following the approval of Libmeldy by the European Commission in December 2020 for the treatment of early onset metachromatic leukodystrophy ("MLD"), characterized by biallelic mutations in the arylsulfatase-A (ARSA) gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

We recognize revenue when control of promised goods is transferred to a customer at an amount that reflects the consideration to which we expect to be entitled in exchange for those goods. Control of the product transfers upon infusion of the product. To determine revenue recognition, we perform the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) we satisfied the performance obligations. We only apply the five-step model to contracts when collectability of the consideration to which we are entitled in exchange for the goods we transfer to the customer is determined to be probable. In certain regions of Europe and the Middle East, we utilize distributors to act in an agent capacity including for patient identification and other related functions. We are exclusively responsible for product fulfillment and retain inventory risk and pricing discretion of the product. Evaluation of these key indicators support our assertion that we maintain control over the product prior to delivery to the patient. We have concluded that we are the principal in these transactions and we record the associated revenue on a gross basis.

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. We do not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. We expense incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of December 31, 2022, we have not capitalized any costs to obtain contracts.

We recognize product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is at a point in time once the patient has been infused. Product revenue is recorded at the net sales price, or transaction price. We record product revenue reserves, which are classified as a reduction in product revenue, to account for the components of variable consideration. Variable consideration includes the following components: government rebates, including performance-based rebates, trade discounts and allowances, and other incentives, which are described below.

These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are classified as a liability. Our estimates of reserves established for variable consideration are calculated based upon an application of the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. These estimates reflect our historical experience, current contractual and statutory requirements, specific known market events and trends, industry data, and current expectations around final pricing. The amount of variable consideration that is included in the transaction price may be subject to constraint and is included in net product revenue only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. Actual amounts of consideration received may ultimately differ from our estimates. If actual results vary, we adjust these estimates, which could have an effect on earnings in the period of adjustment. The following is a summary of the types of variable consideration the Company records:

Government rebates: We are subject to statutory government rebates on sales in certain European countries as well as estimated rebates in certain European countries because final pricing has not yet been negotiated. We record reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of product revenue and a current liability that is included in accrued expenses on our consolidated balance sheet. We are also subject to potential rebates in connection with performance criteria agreed upon with certain payors. The estimate for rebates is based on statutory discount rates, industry pricing data, current expectations around final pricing to be obtained, and historical experience of the performance of our products during clinical trials.

Trade discounts and allowances: We may offer customers discounts, such as prompt pay discounts to remit payment in accordance with the stated terms of the invoice and fees for distribution services. These discounts are explicitly stated in the contracts and recorded in the period the related product revenue is recognized. Our payment terms can range from 30 days to under 1 year. We estimate which customers will earn these discounts and fees and deducts these discounts and fees in full from gross product revenue and accounts receivable at the time we recognize the related revenue.

Product returns: Based on the timing of revenue recognition upon treatment with the patient, we do not expect any returns of our products.

Other incentives: While we do not currently have any other incentives that have been recorded to date, we may enter into future arrangements that have other incentives that will be recorded as a reduction of revenue.

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.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

Interest rate sensitivity

As of December 31, 2022, we had cash, cash equivalents, marketable securities, and restricted cash of $148.0 million. Our exposure to interest rate sensitivity is impacted by changes in the underlying UK and U.S. bank interest rates. Our surplus cash has been invested in corporate bonds, commercial paper, U.S. treasuries, and money market accounts. 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.

We have borrowed $33.0 million under our credit facility. Amounts outstanding under the credit facility bear interest at a variable interest rate of 5.95% plus LIBOR. As of December 31, 2022, the carrying value of the term loans under the credit facility was $32.7 million.

In 2017, the United Kingdom's Financial Conduct Authority announced that after 2021 it would no longer compel banks to submit the rates required to calculate the London Interbank Offered Rate (LIBOR) and other interbank offered rates, which have been widely used as reference rates for various securities and financial contracts, including loans, debt and derivatives. This announcement indicates that the continuation of LIBOR on the current basis is not guaranteed after 2021. Regulators in the U.S. and other jurisdictions have been working to replace these rates with alternative reference interest rates that are supported by transactions in liquid and observable markets, such as the Secured Overnight Financing Rate (SOFR). Currently, our credit facilities reference LIBOR-based rates. In January 2023, we amended and restated our credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

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 expends 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 realized and unrealized foreign currency losses of $24.3 million and $1.2 million for the years ended December

31, 2022 and 2021. These foreign currency transaction gains and losses are included in other (expense) income 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 loss but are included in our foreign currency translation 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 8. Financial Statements and Supplementary Data.

Our consolidated financial statements are appended at the end of this Annual Report, starting at page F-1, and incorporated herein by reference.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

We maintain disclosure controls and procedures (as defined in Rules 13a-15(e) or 15d-15(e) under the Securities Exchange Act of 1934, as amended, or the Exchange Act) that are designed to ensure that information required to be disclosed in reports that we file or submit under the Exchange Act is (1) recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms and (2) accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

Our management, with the participation of our principal executive officer and principal financial officer, evaluated the effectiveness of our disclosure controls and procedures as of the end of the period covered by this report. In designing and evaluating our disclosure controls and procedures, our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Our principal executive officer and principal financial officer have concluded based upon the evaluation described above that, as of December 31, 2022, our disclosure controls and procedures were effective at the reasonable assurance level.

We continue to review and document our disclosure controls and procedures, including our internal controls and procedures for financial reporting, and may from time to time make changes aimed at enhancing their effectiveness and to ensure that our systems evolve with our business in accordance with the Exchange Act.

Management's Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with general accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting based on the 2013 framework in Internal Control – Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on our evaluation under that framework, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

The following summary contains a description of material U.S. federal income tax and UK 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).

Based on the current and expected composition of our income and assets and the value of our assets, we believe that we were a PFIC for U.S. federal income tax purposes for our taxable year ended December 31, 2022. 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.

Because it was possible that we were a PFIC for the 2022 taxable year, we currently expect that we will provide the information necessary for U.S. holders to make a QEF Election. We may elect to provide such information on our website (www.ORTX.com). 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 OUR INVESTORS TO CONSULT THEIR TAX ADVISOR REGARDING THE IMPACT OF OUR PFIC STATUS ON THEIR INVESTMENTS IN OUR ORDINARY SHARES OR ADSs AS WELL AS THE APPLICATION OF THE PFIC RULES TO THEIR INVESTMENT IN OUR 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 2021 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 UK 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.

UK Taxation

The following is intended as a general guide to current UK tax law and HMRC published practice (which is not binding) applying as at the date of this Annual Report on Form 10-K (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 UK 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 UK taxation. It is written on the basis that the company is not (and will not) directly or indirectly at any time derive 75% or more of our qualifying asset value from UK land, and that it is and remains solely resident in the UK for tax purposes and will therefore be subject to the UK 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-UK 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 UK 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 UK 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 UK 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 UK direct tax purposes.

This guide may not relate to certain classes of UK 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 UK taxation on a remittance basis or to whom split year treatment applies.

THESE PARAGRAPHS ARE A SUMMARY OF CERTAIN UK 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-UK RESIDENT OR DOMICILED PERSONS OR PERSONS SUBJECT TO TAXATION IN ANY JURISDICTION OTHER THAN THE UK 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 UK tax.

Income Tax

An individual UK Holder may, depending on his or her particular circumstances, be subject to UK 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 UK 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 UK through a permanent establishment, branch or agency to which the ADSs are attributable. There are certain exceptions for trading in the UK through independent agent, such as some brokers and investment managers.

Dividend income is treated as the top slice of the total income chargeable to UK income tax for an individual UK Holder. An individual UK Holder who receives a dividend in the 2022/2023 tax year will be entitled to a tax-free allowance of £2,000. Income within the dividend allowance counts towards an individual's basic or higher rate limits and may, therefore, affect the level of personal allowance to which they are entitled. Dividend income in excess of this tax-free allowance will (subject to the availability of any income tax personal allowance) be charged at 8.75% to the extent the excess amount falls within the basic rate band, 33.75% to the extent the excess amount falls within the higher rate band, and 39.35% to the extent the excess amount falls within the additional rate band. The UK government has announced that the dividend tax-free allowance of £2,000 will be reduced to £1,000 with effect from April 2023 for the tax year 2023/2024 and to £500 with effect from April 2024 for the tax year 2024/2025 and thereafter.

Corporation tax

A corporate holder of ADSs who is not resident for tax purposes in the United Kingdom should not be chargeable to UK 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 UK Holders should not be subject to UK 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. It should be noted that the exemptions, whilst of wide application, are not comprehensive and are subject to anti-avoidance rules in relation to a dividend. If the conditions for the exemption are not satisfied, or such anti-avoidance provisions apply, or such UK Holder elects for an otherwise exempt dividend to be taxable, UK corporation tax will be chargeable on the amount of any dividends

(at the current rate of 19% for the tax year 2022/2023, rising to 25% in the tax year 2023/2024 for companies with profits of more than £250,000, whilst the rate of 19% will apply to companies with profits not exceeding £50,000 with a tapered rate applying to profits between £50,000 and £250,000).

Chargeable gains

A disposal or deemed disposal of ADSs by a UK Holder may, depending on the UK 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 UK capital gains tax and corporation tax on chargeable gains.

If an individual UK Holder who is subject to UK income tax at either the higher or the additional rate is liable to UK capital gains tax on the disposal of ADSs, the applicable rate will be 20% (for the tax year 2022/2023). For an individual UK Holder who is subject to UK income tax at the basic rate and liable to UK capital gains tax on such disposal, the applicable rate would be 10% (for the tax year 2022/2023), save to the extent that any capital gains when aggregated with the UK Holder's other taxable income and gains in the relevant tax year exceed the unused basic rate tax band. In that case, the rate applicable to the excess would be 20% (for the tax year 2022/2023).

If a corporate UK Holder becomes liable to UK corporation tax on the disposal (or deemed disposal) of ADSs, the main rate of UK corporation tax would apply (currently at 19% for the tax year 2022/2023, rising to 25% in the tax year 2023/2024 for companies with profits of more than £50,000, whilst the rate of 19% will apply to companies with profits not exceeding £250,000 with a tapered rate applying to profits between £50,000 and £250,000).

A holder of ADSs which is not resident for tax purposes in the UK should not normally be liable to UK 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 UK through a branch or agency (or, in the case of a corporate holder of ADSs, through a permanent establishment) to which the ADSs are attributable. However, an individual holder of ADSs who has ceased to be resident for tax purposes in the UK for a period of less than five years and who disposes of ADSs during that period of temporary non-residence may be liable on his or her return to the UK (or upon ceasing to be regarded as resident outside the UK for the purposes of double taxation treaty) to UK 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

As a general rule, no UK stamp duty or stamp duty reserve tax (or SDRT) is payable on the issue of 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 canceled 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.

Clearance Services and Depositary Receipts

Under current UK legislation, an issue or transfer of ordinary shares or an unconditional agreement to transfer ordinary shares to a clearance service or a depositary receipt system (including, 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, in the case of transfers, 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 UK 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.

However, based on current published HMRC practice following European Union 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 in respect of such an issue of ordinary shares and no SDRT or stamp duty is generally payable in respect of such a transfer of ordinary shares where such transfer is an integral part of an issue of share capital. This position was reaffirmed by HMRC in their January 2021 Newsletter where they confirmed that the SDRT 1.5% charge on issues (or transfers integral to capital raising) remained disapplied under the terms of the European Union (Withdrawal) Act 2018 following the end of the transition period and that this would remain the position unless stamp taxes on shares legislation was amended.

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 transferors or participants in the clearance service or depositary receipt system. Specific professional advice should be sought before incurring or reimbursing the costs of a 1.5% charge.

Transfers of ADSs

No UK SDRT or stamp duty is required to be paid in respect of the issue of or an agreement to transfer ADS (including by way of a paperless transfer of ADSs through the facilities of DTC).

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 11. Executive Compensation.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

Item 14. Principal Accounting Fees and Services.

The information required under this item is incorporated herein by reference to our definitive proxy statement for our 2023 annual general meeting to be filed with the U.S. Securities and Exchange Commission.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

The following documents are filed as part of this Annual Report on Form 10-K:

(a) (1) *Financial Statements*:

The financial statements required by this item are submitted in a separate section beginning on page F-1 of this Report, as follows:

(a) (2) *Financial Statement Schedules*:

Not applicable.

(a) (3) *Exhibits*:

The Exhibits which are filed as part of this Annual Report or which are incorporated by reference are set forth in the Exhibit Index hereto.

EXHIBIT INDEX

Exhibit Number	Description	Incorporated by Reference herein from Form or Schedule	Exhibit	File Date	File Number
2.1†	Asset Purchase and License Agreement, 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	2.1	Oct. 4, 2018	333-227698
3.1	Articles of Association of Orchard Therapeutics plc	Form 8-K	3.1	Jun. 19, 2020	001-38722
4.1	Deposit Agreement	Form 20-F	2.1	Mar. 22, 2019	001-38722
4.2*	Amendment No. 1 to Deposit Agreement				001-38722
4.3	Form of American Depositary Receipt (included in Exhibit 4.1)	Form 20-F	2.2	Mar. 22, 2019	001-38722
4.4	Investment and shareholders' agreement between the registrant and the shareholders named therein, dated August 2, 2018, as amended.	Form F-1	10.1	Jun. 3, 2019	333-231916

4.5*	Description of the registrant's securities.				001-38722
4.6	At-the-Market Letter Agreement	Form F-6	(b)	Feb. 10, 2023	001-38722
4.7	Form of Warrant	Form 8-K	4.1	Mar. 6, 2023	001-38722
10.1#	2016 Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan, as amended.	Form F-1	10.2	Oct. 4, 2018	333-227698
10.2#	2018 Share Option and Incentive Plan.	Form 20-F	4.3	Mar. 22, 2019	001-38722
10.3#	2018 Employee Share Purchase Plan.	Form F-1/A	10.10	Oct. 23, 2018	333-227698
10.4#	Forms of award agreements under the 2018 Share Option and Incentive Plan.	Form 10-K	10.13	Feb. 27, 2020	001-38722
10.5#	2019 Short-Term Incentive Plan.	Form 10-Q	10.1	May 7, 2020	001-38722
10.6#	2020 Inducement Equity Plan and forms of award agreements thereunder.	Form S-8	99.2	Aug. 6 2020	333-241646
10.7#	Form of Deed of Indemnity between the registrant and each of its directors and executive officers.	Form F-1	10.6	Oct. 4, 2018	333-227698
10.8	Deed of Novation, 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	10.4	Oct. 4, 2018	333-227698
10.9	Research and Development Collaboration and License Agreement, among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended	Form F-1	10.5	Oct. 4, 2018	333-227698
10.10	Securities Purchase Agreement dated February 4, 2021, among Orchard Therapeutics plc and the Purchasers named therein	Form 10-Q	10.1	May 13, 2021	001-38722
10.11	Lease Agreement, dated April 5, 2022, among 245 Hammersmith Road Nominee Limited, 245 Hammersmith Road Nominee 2 Limited, 245 Hammersmith Road Partnership and Orchard Therapeutics (Europe) Limited	Form 10-Q	10.1	Aug. 4, 2022	001-38722
10.12†	License and Development Agreement, between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended.	Form F-1	10.8	Oct. 4, 2018	333-227698
10.13††	Amendment Nos. 5 and 6 to License and Development Agreement, between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016.	Form 10-Q	10.2	May 7, 2020	001-38722
10.14*	Senior Term Facilities Agreement, dated May 24, 2019, as amended and restated on January 30, 2023, among Orchard Therapeutics plc, the entities listed as original guarantors therein,				001-38722

	MidCap Financial (Ireland) Limited, and the additional lenders party thereto from time to time.				
10.15#	Amended and Restated Employment Agreement, dated October 4, 2022, among Orchard Therapeutics plc, Orchard Therapeutics North America and Frank Thomas	Form 8-K	10.1	Oct. 6, 2022	001-38722
10.16#	Contract of Employment between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, dated January 8, 2018, as amended, effective May 24, 2019.	Form 10-K	10.16	Feb. 27, 2020	001-38722
10.17#	Variation to Contract of Employment, dated March 18, 2020, between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, M.D., Ph.D.	Form 8-K	10.3	Mar. 20, 2020	001-38722
10.18††	Manufacturing and Technology Development Master Agreement, between Orchard Therapeutics (Europe) Limited and MolMed S.p.A., dated July 2, 2020.	Form 10-Q	10.1	Aug. 6, 2020	001-38722
10.19*	Amendment 1 to the Manufacturing and Technology Development Master Agreement, between Orchard Therapeutics (Europe) Limited and AGC Biologics S.p.A. (formerly MolMed S.p.A), dated December 7, 2022				001-38722
10.20	Securities Purchase Agreement dated March 6, 2023, by and among Orchard Therapeutics plc and the Purchasers named therein.	Form 8-K	10.1	Mar. 6, 2023	001-38722
21.1*	List of Subsidiaries.				
23.1*	Consent of PricewaterhouseCoopers LLP, Independent Registered Public Accounting Firm				
31.1*	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.				
31.2*	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.				
32.1*	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.				
32.2*	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.				
101.INS*	Inline XBRL Instance Document (the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document)				

101.SCH*	Inline XBRL Taxonomy Extension Schema Document
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104*	Cover Page Interactive Data File (embedded within the Inline XBRL document).

* Filed herewith.

† Confidential treatment has been granted 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.

†† Portions of this exhibit (indicated by asterisks) were omitted in accordance with the rules of the Securities and Exchange Commission

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

Item 16. Form 10-K Summary

Not applicable.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized.

ORCHARD THERAPEUTICS PLC

Date: March 14, 2023

By: /s/ Bobby Gaspar
Bobby Gaspar
Chief Executive Officer

POWER OF ATTORNEY

We, the undersigned officers and directors of Orchard Therapeutics plc, hereby severally constitute and appoint Bobby Gaspar and Frank E. Thomas, and each of them singly (with full power to each of them to act alone), our true and lawful attorneys-in-fact and agents, with full power of substitution and re-substitution in each of them for him and in his name, place and stead, and in any and all capacities, to sign for us and in our names in the capacities indicated below any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the U.S. Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite or necessary to be done in and about the premises, as full to all intents and purposes as he might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents or any of them, or their or his substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Annual Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Signature	Title	Date
/s/ Bobby Gaspar Bobby Gaspar	Chief Executive Officer and Director (Principal Executive Officer)	March 14, 2023
/s/ Frank E. Thomas Frank E. Thomas	President and Chief Operating Officer (Principal Financial Officer and Principal Accounting Officer)	March 14, 2023
/s/ James A. Geraghty James A. Geraghty	Chairman of the Board of Directors	March 14, 2023
/s/ Steven M. Altschuler Steven M. Altschuler, M.D.	Director	March 14, 2023
/s/ Joanne T. Beck Joanne T. Beck, Ph.D.	Director	March 14, 2023
/s/ John Curnutte John Curnutte, M.D., Ph.D.	Director	March 14, 2023
/s/ Marc Dunoyer Marc Dunoyer	Director	March 14, 2023
/s/ Charles A. Rowland, Jr. Charles A. Rowland, Jr.	Director	March 14, 2023
/s/ Alicia Secor Alicia Secor	Director	March 14, 2023

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, 2022 and 2021, and the related consolidated statements of operations and comprehensive loss, of shareholders equity and of cash flows for the years then ended, 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, 2022 and 2021, and the results of its operations and its cash flows for the years then ended 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. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

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.

Critical Audit Matters

The critical audit matter communicated below is a matter arising from the current period audit of the consolidated financial statements that was communicated or required to be communicated to the audit committee and that (i) relates to accounts or disclosures that are material to the consolidated financial statements and (ii) involved our especially challenging, subjective, or complex judgments. The communication of critical audit matters does not alter in any way our opinion on the consolidated financial statements, taken as a whole, and we are not, by communicating the critical audit matter below, providing a separate opinion on the critical audit matter or on the accounts or disclosures to which it relates.

Accrued External Research and Development Expenses

As described in Notes 2 and 8 to the consolidated financial statements, the Company has entered into various research and development contracts. When billing terms under these contracts do not coincide with the timing of when the work is performed, management is required to make estimates of outstanding obligations to those third parties. Within accrued expenses and other current liabilities, total accrued external research and development expenses amounted to $11.2 million as of December 31, 2022. Any accrual estimates are based on a number of factors, including management's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period.

The principal considerations for our determination that performing procedures relating to accrued external research and development expenses is a critical audit matter are (i) the significant judgment by management in developing the estimate and (ii) a high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating management's factors related to the progress towards completion of the research and development activities, the related invoicing to date under the contracts and communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced.

Addressing the matter involved performing procedures and evaluating audit evidence in connection with forming our overall opinion on the consolidated financial statements. These procedures included, among others, (i) testing management's process for developing the estimate of accrued external research and development expenses, and for a sample of contracts, (ii) evaluating the appropriateness of the methods used by management to develop the estimate; (iii) testing the completeness and accuracy of the underlying data used in the estimate; and (iv) evaluating the reasonableness of management's factors related to the progress towards completion of the research and development activities. Evaluating the reasonableness of management's factors related to the progress towards completion of the research and development activities involved testing, on a sample basis, invoicing to date under the contracts and communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced.

/s/PricewaterhouseCoopers LLP

Boston, Massachusetts
March 14, 2023

We have served as the Company's auditor since 2019.

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

	December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 68,424	$ 55,912
Marketable securities	75,326	164,195
Accounts receivable	8,467	1,480
Prepaid expenses and other current assets	9,986	23,011
Research and development tax credit receivable	5,942	30,723
Total current assets	168,145	275,321
Non-current assets:		
Operating lease right-of-use-assets	22,774	24,316
Property and equipment, net	8,138	4,767
Restricted cash	4,215	4,266
Intangible assets, net	3,560	4,149
Other assets	12,075	9,590
Total non-current assets	50,762	47,088
Total assets	$ 218,907	$ 322,409
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	$ 9,318	$ 10,008
Accrued expenses and other current liabilities	34,437	24,318
Deferred revenue	959	346
Operating lease liabilities	6,424	7,335
Notes payable, current	9,429	786
Total current liabilities	60,567	42,793
Notes payable, long-term	22,991	32,086
Deferred revenue, net of current portion	10,315	12,519
Operating lease liabilities, net of current portion	19,246	19,278
Other long-term liabilities	7,524	5,783
Total liabilities	120,643	112,459
Commitments and contingencies (Note 17)		
Shareholders' equity:		
Ordinary shares, £0.10 par value, authority to allot up to a maximum nominal value of £13,023,851.50 of shares at December 31, 2022 and 2021, respectively; Issued and outstanding — 126,947,225 and 125,674,095 shares at December 31, 2022 and 2021, respectively.	16,419	16,253
Additional paid-in capital	956,711	940,675
Accumulated other comprehensive income	26,018	3,246
Accumulated deficit	(900,884)	(750,224)
Total shareholders' equity	98,264	209,950
Total liabilities and shareholders' equity	$ 218,907	$ 322,409

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)

	For the Year Ended December 31,	
	2022	2021
Product revenue, net	$ 20,610	$ 700
Collaboration revenue	2,045	975
Total revenues	22,655	1,675
Costs and operating expenses		
Cost of product revenue	6,771	226
Research and development	93,847	86,977
Selling, general and administrative	49,125	54,905
Total costs and operating expenses	149,743	142,108
Loss from operations	(127,088)	(140,433)
Other (expense) income:		
Interest income	1,543	412
Interest expense	(3,079)	(2,497)
Other (expense) income, net	(24,410)	(1,238)
Total other (expense) income, net	(25,946)	(3,323)
Net loss before income tax	(153,034)	(143,756)
Income tax (expense) benefit	2,374	(828)
Net loss attributable to ordinary shareholders	$ (150,660)	$ (144,584)
Net loss per share attributable to ordinary shareholders, basic and diluted	$ (1.18)	$ (1.17)
Weighted average number of ordinary shares outstanding—basic and diluted	127,975,062	123,963,762
Other comprehensive income (loss)		
Foreign currency translation adjustment	22,838	3,124
Unrealized loss on marketable debt securities	(66)	(251)
Total other comprehensive income (loss)	22,772	2,873
Total comprehensive loss	$ (127,888)	$ (141,711)

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

Orchard Therapeutics plc
Consolidated Statements of Shareholders' Equity
(In thousands, except share amounts)

	Ordinary shares					
	Shares	Amount	Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
Balance at December 31, 2020	**98,283,603**	**$ 12,507**	**$ 771,194**	**$ 373**	**$ (605,640)**	**$ 178,434**
Share-based compensation expense	—	—	22,536	—	—	22,536
Exercise of share options	1,727,254	224	2,515	—	—	2,739
Issuance of ESPP shares	232,340	30	534	—	—	564
Vesting of restricted share units, net of shares withheld for taxes	64,647	9	(401)	—	—	(392)
Sale of voting and non-voting ordinary shares, net of issuance costs of $6,355	24,115,755	3,310	140,335	—	—	143,645
Ordinary shares issued as part of consulting agreement	22,758	3	(3)	—	—	—
Ordinary shares issued as part of collaboration agreement	1,227,738	170	3,965	—	—	4,135
Foreign currency translation	—	—	—	3,124	—	3,124
Unrealized loss on marketable debt securities	—	—	—	(251)	—	(251)
Net loss	—	—	—	—	(144,584)	(144,584)
Balance at December 31, 2021	**125,674,095**	**$ 16,253**	**$ 940,675**	**$ 3,246**	**$ (750,224)**	**$ 209,950**
Share-based compensation expense	—	—	16,010	—	—	16,010
Exercise of share options	699,234	91	(90)	—	—	1
Issuance of ESPP shares	544,442	72	139	—	—	211
Vesting of restricted share units, net of shares withheld for taxes	24,202	3	(22)	—	—	(19)
Ordinary shares issued as part of consulting agreement	5,252	—	(1)	—	—	(1)
Foreign currency translation	—	—	—	22,838	—	22,838
Unrealized loss on marketable debt securities	—	—	—	(66)	—	(66)
Net loss	—	—	—	—	(150,660)	(150,660)
Balance at December 31, 2022	**126,947,225**	**$ 16,419**	**$ 956,711**	**$ 26,018**	**$ (900,884)**	**$ 98,264**

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

Orchard Therapeutics plc
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities		
Net loss attributable to ordinary shareholders	$ (150,660)	$ (144,584)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,741	2,327
Share-based compensation	16,010	22,536
Non-cash interest expense	372	392
Amortization of provision on loss contract	(274)	(1,037)
Deferred income taxes	(3,283)	1,131
Amortization of premium (discount) on marketable securities	(305)	1,514
Unrealized foreign currency and other non-cash adjustments	23,208	9,687
Changes in operating assets and liabilities:		
Accounts receivable	(7,420)	(624)
Research and development tax credit receivable	22,568	(13,920)
Prepaid expenses, other current assets, and other assets	5,053	(5,209)
Operating leases, right-of-use-assets	5,431	5,938
Accounts payable, accrued expenses, and other current liabilities	13,642	(9,452)
Deferred revenue	(272)	13,122
Other long-term liabilities	2,154	34
Operating lease liabilities	(4,952)	(6,952)
Net cash used in operating activities	$ (75,987)	$ (125,097)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	201,389	234,732
Purchases of marketable securities	(112,281)	(263,878)
Receipt of funds from construction deposit	7,966	216
Payments on intangible assets	—	(887)
Purchases of property and equipment	(6,514)	(2,348)
Net cash provided by (used in) investing activities	$ 90,560	$ (32,165)
Cash flows from financing activities		
Proceeds from modification of credit facility, net of debt issuance costs paid	—	7,375
Proceeds from employee equity plans	212	3,303
Payment of taxes on restricted stock vesting	(19)	(392)
Proceeds from issuance of shares as part of collaboration agreement	—	4,135
Proceeds from the issuance of ordinary shares in private placement	—	150,000
Payment of placement agent fees and offering costs	(100)	(6,355)
Repayment of notes payable	(786)	—
Net cash (used in) provided by financing activities	$ (693)	$ 158,066
Effect of exchange rate changes on cash	(1,419)	(27)
Net increase in cash, cash equivalents and restricted cash	$ 12,461	$ 777
Cash, cash equivalents, and restricted cash —beginning of year	60,178	59,401
Cash, cash equivalents, and restricted cash —end of year	$ 72,639	$ 60,178
Supplemental disclosure of non-cash activities		
Intangible assets and property and equipment in accounts payable and accrued expenses	60	2,589
Supplemental disclosure of cash flow information		
Lease assets obtained in exchange for new operating lease liabilities	4,912	552
Changes to operating lease right-of-use assets and liabilities from amendments	530	—
Cash paid for interest	2,648	2,103
Cash paid for taxes	157	1,651

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

1. Nature of the Business and Liquidity

Orchard Therapeutics plc (the "Company") is a global gene therapy company dedicated to transforming the lives of people affected by severe diseases through the development of innovative, potentially curative gene therapies. The Company's *ex vivo* autologous hematopoietic stem cell ("HSC") gene therapy approach utilizes genetically modified blood stem cells and seeks to correct the underlying cause of disease in a single administration. The Company has a portfolio that includes a commercial-stage product and research and development-stage product candidates.

The Company is a public limited company incorporated pursuant to the laws of England and Wales. The Company has American Depositary Shares ("ADSs") registered with the U.S. Securities and Exchange Commission (the "SEC"). The ADSs were listed on the Nasdaq Global Select Market on October 31, 2018 and were transferred to the Nasdaq Capital Market on September 13, 2022. As of December 31, 2022, each holder of ordinary shares and ADSs 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. The Company did not declared any dividends in 2022 or 2021.

Effective March 10, 2023, the Company enacted a ratio change wherein each ADS listed on the Nasdaq Capital Market is worth ten ordinary shares.

On February 9, 2021, the Company issued and sold (i) 20,900,321 ordinary shares, nominal value £0.10 per share, at a purchase price of $6.22 per share (the "Purchase Price"), which was the closing sale price of the Company's ADSs on the Nasdaq Global Select Market on February 4, 2021, and (ii) 3,215,434 non-voting ordinary shares, nominal value £0.10 per share, at the Purchase Price (together (i) and (ii) the "2021 Private Placement"). The 2021 Private Placement resulted in net proceeds to the Company of $143.6 million after deducting placement agent fees of $6.0 million and other issuance costs of $0.4 million. As of December 31, 2021, all outstanding non-voting shares have been converted to voting ordinary shares.

In January 2022, the Company began to generate revenue from product sales of Libmeldy™ in Europe following the approval of Libmeldy by the European Commission in December 2020 for the treatment of early onset metachromatic leukodystrophy ("MLD"), characterized by biallelic mutations in the arylsulfatase-A ("ARSA") gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

On March 6, 2023, the Company entered into a Securities Purchase Agreement pursuant to which the Company agreed to sell ordinary shares, non-voting ordinary shares, and warrants to purchase to purchase ordinary shares or non-voting ordinary shares in an unregisterd offering (the "2023 Private Placement"). The 2023 Private Placement consists of two closings. On March 10, 2023, the Company completed the initial closing and issued and sold (i) 56,666,900 ordinary shares and non-voting ordinary shares, nominal value £0.10 per share and (ii) warrants to purchase an aggregate of 62,333,590 ordinary shares or non-voting ordinary shares, at a purchase price of $6.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The initial closing of the 2023 Private Placement resulted in gross proceeds of approximately $34.0 million. Refer to Footnote 19 for further discussion around the 2023 Private Placement.

The Company's business is subject to risks and uncertainties common to development-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 biotechnology 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 in gaining regulatory approval, it is uncertain when, if ever, the Company will realize significant revenue from product sales. The future developments of the COVID-19 pandemic may also directly or indirectly impact the Company's business, including impacts due to travel restrictions, supply chain disruptions, business closures, and other measures.

Through December 31, 2022, the Company funded its operations with proceeds from the sale of equity securities, including ADSs in the Company's initial public offering ("IPO") and follow-on offering, ordinary shares in the private placement, and convertible preferred shares. The Company has also financed its operations through proceeds from the Company's senior term facilities agreement with MidCap Financial (Ireland) Limited, research grants from the California Institute of Regenerative Medicine ("CIRM"), upfront payments from the Company's collaboration agreement and share purchase agreement with Pharming Group N.V., proceeds from the sales of the Company's Libmeldy product, and reimbursements associated with two UK research and development tax relief programs, the Small and Medium-sized Enterprises research and

development tax credit (“SME”) program and the Research and Development Expenditure (“RDEC”) program. The Company has incurred recurring losses since its inception and expects to continue to generate operating losses for the foreseeable future.

The Company expects that its cash, cash equivalents, and marketable securities on hand as of December 31, 2022, of $143.8 million, together with expected proceeds from sales of Libmeldy and the $34 million received in March 2023 from the 2023 Private Placement, will be sufficient to fund its operations and capital expenditure requirements for at least twelve months from the date of filing of this Annual Report on Form 10-K. The Company will seek additional funding through private or public equity financings, debt financings, collaborations, strategic alliances, and marketing, distribution or licensing arrangements. The Company may not be able to obtain financing on acceptable terms, or at all, and may not be able to enter into collaborations or other arrangements. The terms of any financing may adversely affect the holdings or the rights of the Company's stockholders. The future 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.

2. Summary of Significant Accounting Policies

Basis of presentation

The accompanying consolidated financial statements have been prepared in conformity with U.S. generally accepted accounting principles ("GAAP") and include the accounts of the Company and its wholly owned subsidiaries, after elimination of all intercompany accounts and transactions. Any reference in these notes to applicable guidance is meant to refer to authoritative United States generally accepted accounting principles as found in the Accounting Standards Codification (“ASC”) and as amended by Accounting Standards Updates (“ASU”) of the Financial Accounting Standards Board (“FASB”).

Amounts reported are based in thousands, except percentages, per share amounts or as otherwise noted. As a result, certain totals may not sum due to rounding.

Principles of consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Use of estimates

The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, share-based compensation, collaboration agreement milestones, variable consideration in revenue recognition, operating lease assets and liabilities, and income taxes. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company’s estimates.

Concentration of credit risk and of significant suppliers

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, cash equivalents, marketable securities, and receivables.

The Company invests its excess cash, in line with its investment policy, in money market funds and high credit quality debt instruments. The Company's cash is deposited 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.

The Company is dependent upon a third-party contract manufacturer to develop, manufacture, and supply certain raw materials and conduct manufacturing activities for certain research and development and commercial programs. The disruption of the supply of raw materials and manufacturing activities could adversely affect the Company's operations. The

Company believes that its relationship with this manufacturer is satisfactory and has contingency plans in place to mitigate any adverse effects around the loss of this contract manufacturer.

Foreign currency

The financial statements of the Company's subsidiaries with functional currencies other than the U.S. Dollar are translated into U.S. Dollars using period-end exchange rates for assets and liabilities, historical exchange rates for shareholders' equity and weighted average exchange rates for operating results. Unrealized losses are driven primarily by intercompany balances denominated in currencies other than the functional currency of the entity with the intercompany balance, and typically fluctuates concurrently with fluctuations in the U.S. Dollar, Pounds sterling, and Euro exchange rates. Translation gains and losses are included in accumulated other comprehensive income (loss) in shareholders' equity. Foreign currency transaction gains and losses are included in other income (expense), net in the results of operations. The Company recorded realized and unrealized foreign currency transaction losses of $24.3 million and of $1.2 million for the years ended December 31, 2022 and 2021, respectively, which is included in other income (expense) in the statements of operations and comprehensive loss.

Segment information

The Company operates in a single segment focusing on researching, developing and commercializing potentially curative gene therapies. Consistent with its operational structure, its chief operating decision maker manages and allocates resources at a global, consolidated level. Therefore, the results of the Company's operations are reported on a consolidated basis for the purposes of segment reporting.

All material long-lived assets of the Company reside in the United States or United Kingdom. The Company had property and equipment, net, of $7.5 million and $0.6 million located in the United Kingdom and United States, respectively, as of December 31, 2022. The Company had property and equipment, net, of $3.6 million and $1.2 million located in the United Kingdom and United States, respectively, as of December 31, 2021. The Company had right-of-use assets in the United States and United Kingdom of $11.2 million and $11.6 million, respectively, as of December 31, 2022. The Company had right-of-use assets in the United States and United Kingdom and European Union of $12.5 million and $11.8 million, respectively, as of December 31, 2021.

Cash equivalents

The Company considers all highly liquid investments purchased with original maturities of 90 days or less at the date of acquisition to be cash equivalents.

Marketable securities

Marketable securities consist of investments with original maturities greater than ninety days from the date of acquisition. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company considers its investment portfolio of investments as available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices or other observable inputs. Unrealized gains and losses are recorded as a component of other comprehensive income (loss). Realized gains and losses are determined on a specific identification basis and are included in other income (loss). Amortization and accretion of discounts and premiums is also recorded in other income (loss).

When the fair value is below the amortized cost of the asset an estimate of expected credit losses is made, the estimate is limited to the amount by which fair value is less than amortized cost. The credit-related impairment amount is recognized in the consolidated statements of operations and the remaining impairment amount and unrealized gains are reported as a component of accumulated other comprehensive income (loss) in shareholders' equity. Credit losses are recognized through the use of an allowance for credit losses account and subsequent improvements in expected credit losses are recognized as a reversal of the allowance account. If the Company has the intent to sell the security or it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis the allowance for credit loss is written off and the excess of the amortized cost basis of the asset over its fair value is recorded in the consolidated statements of operations.

Accounts receivable

Accounts receivable arise from product revenue and amounts due from the Company's collaboration partners and have payment terms that generally require payment within 30 to 90 days. For some Libmeldy customers, our payment terms can range from 30 days to under one year. The amount from product revenue represents amounts due from distributors in Europe, which are recorded net of reserves for trade discounts and allowances, and other incentives to the extent such amounts are payable to the customer by the Company. The Company monitors economic conditions to identify facts or circumstances that

may indicate that its receivables are at risk of collection. The Company provides reserves against accounts receivable for estimated losses, if any, that may result from a customer's inability to pay based on the composition of its accounts receivable, current economic conditions, and historical credit loss activity. Amounts determined to be uncollectible are charged or written-off against the reserve. The Company did not record any expected credit losses related to outstanding accounts receivable in 2022 and 2021.

Fair Value Measurements

Certain assets and liabilities of the Company are carried at fair value under GAAP. 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—Valuations based on quoted prices in active markets for identical assets or liabilities that the Company has the ability to access at the measurement date.

Level 2—Valuations based on quoted prices for similar assets or liabilities in markets that are not active or for which all significant inputs are observable, either directly or indirectly, such as quoted market prices, interest rates, and yield curves.

Level 3—Valuations that require inputs that reflect the Company’s own assumptions that are both significant to the fair value measurement and unobservable.

To the extent a valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair values requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized as 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 Company believes that the carrying amount reflected on the consolidated balance sheets for research and development tax incentive receivable, trade receivables, accounts payable, and accrued expenses approximate fair value due to their short-term maturities. The carrying value of the Company’s outstanding notes payable approximates fair value (a Level 2 fair value measurement), reflecting interest rates currently available to the Company

Restricted cash and construction deposits

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 the Company's consolidated balance sheets. The Company has an outstanding letter of credit for $3.0 million associated with a lease and is required to hold this amount in a standalone bank account as of December 31, 2022 and 2021. The Company is also contractually required to maintain a cash collateral account associated with corporate credit cards and other leases in the amount of $1.3 million as of December 31, 2022 and 2021.

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. The following table provides a reconciliation of cash, cash equivalents, and restricted cash reported in the consolidated balance sheet that sum to the total of the amounts reported in the consolidated statement of cash flows (in thousands):

	As of December 31,	
	2022	2021
Cash and cash equivalents	$ 68,424	$ 55,912
Restricted cash	4,215	4,266
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	$ 72,639	$ 60,178

Inventory

The Company began capitalizing inventory manufactured or purchased after the acquisition of Strimvelis in April 2018 and EMA approval of Libmeldy in December 2020. Inventory is stated at the lower of cost or estimated net realizable value with cost determined on a first-in, first-out basis. Inventory costs include raw materials, third-party contract manufacturing, third-party packaging services, and freight. Raw and intermediate materials that may be utilized for either research and development or commercial purposes are classified as inventory. Amounts in inventory that are used for research and development purposes are charged to research and development expense when the product enters the research and development process and can no longer be used for commercial purposes and, therefore, does not have an “alternative future use” as defined in authoritative guidance. The Company performs an assessment of the recoverability of capitalized inventory during each reporting period and, if needed, writes down any excess and obsolete inventory to its estimated net realizable

value in the period it is identified. If they occur, such impairment charges are recorded as a component of cost of goods sold in the consolidated statements of operations and comprehensive income (loss). Inventory is included in prepaid expenses and other current assets on the consolidated balance sheets as its balance was not significant as of December 31, 2022 or 2021 (refer to Footnote 4).

Prior to the initial date that regulatory approval is received, costs related to the production of inventory are recorded as research and development expense on the Company's consolidated statements of operations and comprehensive income (loss) in the period incurred.

Intangible assets, net

Intangible assets consist of milestones associated with the Company's approved products net of accumulated amortization. The Company amortizes its intangible assets using the straight-line method over their estimated economic lives and periodically reviews for impairment. The Company has not recognized any impairment charges related to intangible assets to date.

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.

Asset Type:	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

Repairs and maintenance expenditures, which are not considered improvements and do not extend the useful life of property and equipment, are expensed as incurred. 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 consolidated statements of operations and other comprehensive loss.

Impairment of long-lived assets

Long-lived assets consist of property and equipment and operating lease right-of-use assets. 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 or asset group may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant under performance 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 or asset group to its carrying value. An impairment loss would be recognized when the 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.

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 and benefits, share-based compensation, facilities costs, depreciation, third-party license fees, certain milestone payments, external costs incurred by outside vendors engaged to conduct clinical development activities and clinical trials, the purchase of in-process research and development assets, and costs incurred to develop a manufacturing process, perform analytical testing and 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, 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 expenses on the basis of costs incurred on the research program. Royalties to third parties associated with our research grants will be accrued when they become probable.

Accrued external research and development expenses

The Company has entered into various research and development contracts. These agreements are cancelable, and related costs are recorded as research and development expenses as incurred. When billing terms under these contracts do not coincide with the timing of when the work is performed, the Company is required to make estimates of outstanding obligations to those third parties. Any accrual estimates are based on a number of factors, including the Company's knowledge of the progress towards completion of the research and development activities, invoicing to date under the contracts, communication from the research institution or other entities of any actual costs incurred during the period that have not yet been invoiced, and the costs included in the contracts. Significant judgments and estimates may be made in determining the accrued balances at the end of any reporting period. 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. Actual results could differ from the estimates made by the Company. The historical accrual estimates made by the Company have not been materially different from the actual costs.

Share-based compensation

The Company measures all stock options and other stock-based awards granted based on the fair value of the award on the date of the grant and recognizes stock-based compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. The Company has elected to recognize forfeitures as they occur. Therefore, the reversal of compensation cost previously recognized for an award that is forfeited because of a failure to satisfy a service or performance condition is recognized in the period of the forfeiture. The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipients' service payments are classified.

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option pricing model, which requires inputs based on certain subjective assumptions, including the fair value of the Company's common stock, expected stock price volatility, the expected term of the stock option, the risk-free interest rate for a period that approximates the expected term of the stock option, and the Company's expected dividend yield. The risk-free interest rate is based on a U.S. treasury instrument whose term is consistent with the expected term of the stock options. The expected term of the Company's options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including those in the early stages of product development with a similar and therapeutic focus. For these analyses, the Company selects companies with comparable characteristics to its own including enterprise value, risk profiles, position within the industry, and with historical share price information sufficient to meet the expected term of the options/ The closing sale price per share of the Company's common stock as reported on The Nasdaq Global Market on the date of grant is used to determine the fair value, which is then used to establish the exercise price per share of share-based awards to purchase common stock.

Comprehensive loss

Comprehensive loss is composed of net loss and other comprehensive income (loss). Other comprehensive income (loss) consists of unrealized gains and losses on marketable securities and foreign currency translation gains and losses.

Leases

At the inception of an arrangement, the Company determines whether the arrangement is or contains a lease based on specific facts and circumstances, the existence of an identified asset(s), if any, and the Company's control over the use of the identified asset(s), if applicable. Operating lease assets represent a right to use an underlying asset for the lease term and operating lease liabilities represent an obligation to make lease payments arising from the lease. Operating lease liabilities with a term greater than one year and their corresponding right-of-use assets are recognized on the balance sheet at the commencement date of the lease based on the present value of lease payments over the expected lease term. The Company recognizes a corresponding right-of-use ("ROU") asset, initially measured as the amount of lease liability, adjusted for any initial lease costs or lease payments made before or at the commencement of the lease, and reduced by any lease incentives. The Company made an accounting policy election to not record a right-of-use asset or lease liability for leases with a term of one year or less. To date, the Company has not identified any material short-term leases, either individually or in the aggregate.

The lease liability is measured at the present value of future lease payments, discounted using the discount rate as of the lease commencement date. Future lease payments may include payments that depend on an index or a rate (such as the consumer price index or other market index). The Company initially measures payments based on an index or rate by using the applicable rate at lease commencement and subsequent changes in such rates are recognized as variable lease costs. Variable payments that do not depend on a rate or index are not included in the lease liability and are recognized as they are incurred. The Company's contracts typically do not have variable payments based on index or rate.

When readily determinable, the discount rate used to calculate the lease liability is the rate implicit in the lease. As the Company's leases do not typically provide an implicit rate, the Company utilizes an incremental borrowing rate, which is the rate incurred to borrow an amount on a collateralized basis over a similar term as the associated lease in a similar economic environment. The Company estimated the incremental borrowing rate based on the Company's currently outstanding credit facility as inputs to the analysis to calculate a spread, adjusted for factors that reflect the profile of secured borrowing over the expected term of the lease. The lease term used to calculate the lease liability includes options to extend or terminate the lease when it is reasonably certain that the Company will exercise that option. With limited exceptions, the nature of the Company's facility leases is such that there are no economic or other conditions that would indicate that it is reasonably certain at lease commencement that the Company will exercise options to extend the term.

The components of a lease should be split into three categories: lease components (e.g., land, building, etc.), non-lease components (e.g., common area maintenance, utilities, performance of manufacturing services, purchase of inventory, etc.), and non-components (e.g., property taxes, insurance, etc.). Then the fixed contract consideration (including any related to non-components) must be allocated based on fair values to the lease components and non-lease components. Although separation of lease and non-lease components is required, certain accounting policy elections are available to entities. Entities can elect accounting policies that would not separate lease and non-lease components. Rather, they would account for each lease component and the related non-lease component together as a single component. The Company has elected not to apply the accounting policy with respect to its lease of manufacturing space at a contract manufacturing organization, and as a result, the Company has allocated the consideration between the lease and non-lease components of the contract based on the respective fair values of the lease and non-lease components. The Company calculated the fair value of the lease and non-lease components using financial information readily available as part of its master services arrangement and other representative data indicative of fair value.

The Company's leases consist of only operating leases. Operating leases are recognized on the balance sheet as ROU assets, operating lease liabilities, and operating lease liabilities non-current. Fixed payments are included in the calculation of the lease balances while certain variable costs paid for certain operating and pass-through costs are excluded. Lease expense is recognized over the expected lease term on a straight-line basis.

The Company accounts for sublease income on a straight-line basis over the respective lease period and records an unbilled rent receivable for sublease income incurred but not yet paid. The Company periodically performs a collectability assessment associated with any unbilled rent receivables. The Company recognizes the sublease income as a reduction to the related operating expense associated with the head lease.

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. 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 initially recorded a liability associated with the loss contract of $18.4 million in 2018. The Company recognizes the amortization of the loss provision on a diminishing balance basis based on the actual net loss incurred associated with the Strimvelis program 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 reduction to research and development expense. The Company

has made an estimate of the expected future losses associated with Strimvelis and will adjust this estimate as facts and circumstances change regarding the commercial availability and costs of maintaining and selling Strimvelis. The Company does not update the accrued loss provision for any subsequent adjustment of future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for updated future losses.

The following table below outlines the changes to the Strimvelis loss provision for the periods ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
Balance at beginning of period	$ 3,419	$ 4,482
Amortization of loss provision	(274)	(1,037)
Foreign currency translation	(326)	(26)
Balance at end of period	$ 2,819	$ 3,419

As of December 31, 2022, the entire balance of the Strimvelis loss provision was categorized as current. As of December 31, 2021, $0.7 million of the loss provision was classified as current, and $2.7 million was classified as non-current.

United Kingdom Research and development income tax credits

As the Company carries out research and development activities, it is able to submit tax credit claims from two UK research and development tax relief programs: the Small and Medium-Sized Enterprises research and development tax credit ("SME") program and the Research and Development Expenditure Credit ("RDEC"), depending on eligibility. 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.

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. Each reporting period, the Company assesses its research and development activities and expenditures to determine whether the nature of these costs will qualify for credit under the tax relief programs and whether the claims will ultimately be realized based on the allowable reimbursable expense criteria established by the UK government. The Company expects a proportion of expenditures incurred in relation to its pipeline research, clinical trials management, and manufacturing development activities to be eligible for the research and development tax relief programs for the year ended December 31, 2022. The Company has qualified under the more favorable SME regime for the year ended December 31, 2021 and expects to qualify under the SME regime for the year ending December 31, 2022.

The Company recognizes credits from the research and development incentives when the relevant expenditure has been incurred and there is reasonable assurance that the reimbursement will be received. Such credits are accounted for as reductions in research and development expenses. The following table outlines the changes to the research and development tax credit receivable, including amount recognized as an offset to research and development expense during the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
Balance at beginning of period	$ 30,723	$ 17,344
Recognition of credit claims as offset to research and development expense	8,243	13,920
Receipt of credit claims	(30,811)	-
Foreign currency translation	(2,213)	(541)
Balance at end of period	$ 5,942	$ 30,723

As of December 31, 2022 and 2021, the Company's tax credit receivable was classified as current with receipt of the credit expected within twelve months of the balance sheet date.

Income taxes

The Company is primarily subject to corporation taxes in the United Kingdom, the United States, and certain European Union countries in which it has legal subsidiaries. The calculation of the Company's tax provision involves the application of country applicable tax law and requires judgment and estimates.

The Company accounts for income taxes in accordance with ASC Topic 740, *Accounting for Income Taxes*, which provides for deferred taxes using an asset and liability approach. The Company recognizes deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements or tax returns. The Company determines its deferred tax assets and liabilities based on differences between financial reporting and tax bases of assets and

liabilities, which are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. Valuation allowances are provided if, based upon the weight of available evidence, it is more likely than not that some or all of the net deferred tax assets will not be realized.

The Company accounts for uncertainty in income taxes 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.

Product revenue, net

Libmeldy

In January 2022, the Company began generating product revenue from sales of Libmeldy in Europe following the approval of Libmeldy by the European Commission in December 2020 for the treatment of early onset MLD, characterized by biallelic mutations in the ARSA gene leading to a reduction of the ARSA enzymatic activity in children with (i) late infantile or early juvenile forms, without clinical manifestations of the disease, or (ii) the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline.

The Company recognizes revenue when control of promised goods is transferred to a customer at an amount that reflects the consideration to which the Company expects to be entitled in exchange for those goods. Control of the product transfers upon infusion of the product.

To determine revenue recognition, the Company performs the following five steps: (i) identify the contract(s) with a customer; (ii) identify the performance obligations in the contract; (iii) determine the transaction price, including variable consideration, if any; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when (or as) the Company satisfies the performance obligations. The Company only applies the five-step model to contracts when collectability of the consideration to which it is entitled in exchange for the goods the Company transfers to the customer is determined to be probable.

In certain regions of Europe and the Middle East, the Company utilizes distributors to act in an agent capacity including for patient identification and other related functions. The Company is exclusively responsible for product fulfillment and retains inventory risk and pricing discretion of the product. Evaluation of these key indicators supports the assertion that the Company maintains control over the product prior to delivery to the patient. The Company has concluded that it is the principal in these transactions and records the associated revenue on a gross basis with any payments to these entities being recorded as a selling expense.

Amounts are recorded as accounts receivable when the right to the consideration is unconditional. The Company does not assess whether a contract has a significant financing component if the expectation at contract inception is that the period between payment by the customer and the transfer of the promised goods or services to the customer will be one year or less. The Company expenses incremental costs of obtaining a contract as and when incurred if the expected amortization period of the asset that would have been recognized is one year or less or the amount is immaterial. As of December 31, 2022, the Company has not capitalized any costs to obtain contracts.

The Company recognizes product revenue, net of variable consideration related to certain allowances and accruals, when the customer takes control of the product, which is at a point in time once the patient has been infused. Product revenue is recorded at the net sales price, or transaction price. The Company records estimated product revenue reserves, which are classified as a reduction in product revenue, to account for the components of variable consideration. Variable consideration includes the following components: government rebates, including performance-based rebates, trade discounts and allowances, and other incentives, which are described below.

These reserves are based on estimates of the amounts earned or to be claimed on the related sales and are classified as a liability. The Company's estimates of reserves established for variable consideration are calculated based upon an application of the expected value method, which is the sum of probability-weighted amounts in a range of possible consideration amounts. These estimates reflect the Company's historical experience, current contractual and statutory requirements, specific known market events and trends, industry data, and current expectations around final pricing. The amount of variable consideration that is included in the transaction price may be subject to constraint and is included in net product revenue only to the extent that it is probable that a significant reversal in the amount of the cumulative revenue recognized will not occur in a future period. The actual amounts of consideration received may ultimately differ from the Company's estimates. If actual results vary, the Company adjusts these estimates, which could have an effect on earnings in the period of adjustment. The following is a summary of the types of variable consideration the Company records:

Government rebates: The Company is subject to statutory government rebates on sales in certain European countries as well as estimated rebates in certain European countries because final pricing has not yet been negotiated. The Company records reserves for rebates in the same period the related product revenue is recognized, resulting in a reduction of product revenue and a current liability that is included in accrued expenses on the Company's consolidated balance sheet. The Company is also subject to potential rebates in connection with performance criteria agreed upon with certain payors. The estimate for rebates is based on statutory discount rates, industry pricing data, current expectations around final pricing to be obtained, and historical experience of the performance of the Company's products during clinical trials. The Company classifies rebates within accrued expenses in the accompanying consolidated balance sheets.

Trade discounts and allowances: The Company may offer customers discounts, such as prompt pay discounts to remit payment in accordance with the stated terms of the invoice. These discounts are explicitly stated in the contracts and recorded in the period the related product revenue is recognized. The Company estimates which customers will earn these discounts and fees and deducts these discounts and fees in full from gross product revenue and accounts receivable at the time the Company recognizes the related revenue. The Company classifies trade discounts and allowances as a reduction of accounts receivable within the accompanying consolidated balance sheets.

Product returns: Based on the timing of revenue recognition upon treatment with the patient, the Company does not expect any returns of the Company's products.

Other incentives: While the Company does not currently have any other incentives that have been recorded to date, the Company may enter into future arrangements that have other incentives that will be recorded as a reduction of revenue.

Strimvelis

The Company's product sales of Strimvelis are currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. The hospital will purchase and pay for the products and submit a claim to the payer. The Company's contracted sales with the hospital contains a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation, which is upon transferring control of the products to the hospital. The Company evaluated the variable consideration under ASC 606 and there is currently no variable consideration included in the transaction price for the products. Costs to manufacture and deliver the product and those associated with administering the therapy are included in the cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates there is limited risk of product return, including the risk of product expiration.

Collaboration revenue

The terms of the Company's collaboration agreements may include consideration such as non-refundable license fees, funding of research and development services, payments due upon the achievement of clinical and pre-clinical performance-based development milestones, regulatory milestones, manufacturing services, sales-based milestones and royalties on product sales.

The Company first evaluates collaboration arrangements to determine whether the arrangement (or part of the arrangement) represents a collaborative arrangement pursuant to ASC Topic 808, *Collaborative Arrangements*, based on the risks and rewards and activities of the parties pursuant to the contractual arrangement. The Company accounts for any collaborative arrangement or elements within the contract that are deemed to be a collaborative arrangement, and not a customer relationship, in accordance with ASC 808. Through December 31, 2022, the Company entered into one agreement with Pharming Group N.V. (the "Pharming Agreement", see Note 16) that is accounted for pursuant to ASC 606 five-step model.

The Company recognizes the transaction price allocated to upfront license payments as revenue upon delivery of the license to the customer and resulting ability of the customer to use and benefit from the license, if the license is determined to be distinct from the other performance obligations identified in the contract. If the license is considered to not be distinct from other performance obligations, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied (i) at a point in time, but only for licenses determined to be distinct from other performance obligations in the contract, or (ii) over time, and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue from license payments. The Company evaluates the measure of progress each reporting period and, if necessary, adjusts the measure of performance and related revenue recognition.

The Pharming Agreement entitles the Company to additional payments upon the achievement of performance-based milestones. These milestones are generally categorized into three types: development milestones, regulatory milestones, and sales-based milestones. The Company is also eligible to receive from Pharming tiered royalty payments on worldwide net sales. The Company evaluates whether it is probable that the consideration associated with each milestone will not be subject to a significant reversal in the cumulative amount of revenue recognized. Amounts that meet this threshold are included in the

transaction price using the most likely amount method, whereas amounts that do not meet this threshold are considered constrained and excluded from the transaction price until they meet this threshold. Milestones tied to regulatory approval, and therefore not within the Company's control, are considered constrained until such approval is received. Upfront and ongoing development milestones per the collaboration agreements are not subject to refund if the development activities are not successful. At the end of each subsequent reporting period, the Company re-evaluates the probability of a significant reversal of the cumulative revenue recognized for the milestones, and, if necessary, adjusts the estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis, which would affect revenues from collaborators in the period of adjustment.

The Company may enter into an agreement that includes sales-based milestone payments and royalties in exchange for a license of intellectual property. The Company considers the underlying facts and circumstances of these agreements, noting whether the future payments are contingent upon future sales and whether they are dependent on a third party's ability to successfully commercialize a product using the licensed intellectual property. The Company also considers whether the license is the only, or predominant, item to which the milestone payments and royalties relate. If the Company concludes the license is the predominant item in the agreement, therefore the primary driver of value, the Company excludes sales-based milestone payments and royalties from the transaction price until the sale occurs (or, if later, until the underlying performance obligation to which some or all of the royalty has been allocated has been satisfied or partially satisfied). Currently, the Company has not recognized any royalty revenue resulting from the Pharming Agreement.

ASC 606 requires the Company to allocate the arrangement consideration on a relative standalone selling price basis for each performance obligation after determining the transaction price of the contract and identifying the performance obligations to which that amount should be allocated. The relative standalone selling price is defined in ASC 606 as the price at which an entity would sell a promised good or service separately to a customer. If other observable transactions in which the Company has sold the same performance obligation separately are not available, the Company is required to estimate the standalone selling price of each performance obligation. Key assumptions to determine the standalone selling price may include forecasted revenues, development timelines, reimbursement rates for personnel costs, discount rates and probabilities of technical and regulatory success.

Whenever the Company determines that a contract should be accounted for as a combined performance obligation, which is recognized over time, it will utilize the cost-to-cost input method. Revenue will be recognized over time using the cost-to-cost input method, based on the total estimated costs to fulfill the obligations. The Company will recognize revenue as services are delivered. Significant management judgment is required in determining the estimate of total costs required under an arrangement and the period over which the Company is expected to complete its performance obligations under an arrangement.

Consideration that does not meet the requirements to satisfy the above revenue recognition criteria is a contract liability and is recorded as deferred revenue in the consolidated balance sheets. Short-term deferred revenue consists of amounts that are expected to be recognized as revenue in the next 12 months. Amounts that the Company expects will not be recognized within the next 12 months are classified as long-term deferred revenue.

The Company recognizes as revenue the amount of the transaction price that is allocated to the respective performance obligation when (or as) each performance obligation is satisfied, either at a point in time or over time. In particular, for the Company's collaborations with Pharming, revenue attributable to research services is recognized as those services are provided, based on the costs incurred to date.

Net loss per share

Basic net loss per share is computed by dividing the net loss by the weighted average number of ordinary shares outstanding for the period. Diluted net loss is computed by adjusting net loss based on the potential impact of dilutive securities. Diluted net loss per share is computed by dividing the diluted net loss by the weighted average number of ordinary shares outstanding for the period, including potentially dilutive ordinary shares. For the purpose of this calculation, outstanding options and unvested restricted shares are considered potential dilutive ordinary shares. Since the Company was in a loss position for all periods presented, the basic net loss per share is the same as diluted net loss per share for all periods as the inclusion of all potential ordinary share equivalents 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:

	As of December 31,	
	2022	2021
Share options	13,076,959	14,042,781
Unvested restricted incentive shares	2,253,199	512,908
	15,330,158	14,555,689

Recent accounting pronouncements

In November 2021, the FASB issued ASU No. 2021-10, *Government Assistance (Topic 832): Disclosures by Business Entities about Government Assistance*, which requires increased transparency in the disclosures about government assistance in the notes to the financial statements. This ASU is effective for the Company beginning January 1, 2022, and interim periods within that year, with early adoption permitted. The Company adopted and applied the amendments of this ASU to its disclosures. The application of this ASU did not have a material impact on the Company's financial position, results of operations or cash flows.

In March 2020, the FASB issued ASU 2020-04, Reference Rate Reform (Topic 848)*: Facilitation of the Effects of Reference Rate Reform on Financial Reporting* and issued two subsequent amendments: ASU 2021-01, issued in January 2021, refines the scope of ASU and clarifies some of its guidance as part of the FASB's monitoring of global reference rate reform activities and ASU 2022-06, issued in December 2022, which extends the effective period of the ASU through December 31, 2023 (collectively, including ASU 2020-04, "ASC 848"). ASC 848 provides temporary optional expedients and exceptions to the GAAP guidance on contract modifications and hedge accounting to ease the financial reporting burdens related to the expected market transition from the London Interbank Offered Rate ("LIBOR") and other interbank offered rates to alternative reference rates. ASC 848 is effective for all entities as of March 12, 2020, through December 31, 2023, at which time transition is expected to be complete. The Company is currently reviewing the provisions of this pronouncement, specifically its impact on its notes payable, but does not expect this guidance will have a material impact on the Company's consolidated financial statements.

3. Fair Value Measurements and Marketable Securities

The following tables present information about the Company's financial assets that have been measured at fair value as of December 31, 2022 and 2021, and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value (in thousands):

	Fair Value Measurements as of December 31, 2022			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 1,239	$ —	$ —	$ 1,239
U.S. treasuries	—	6,600	—	6,600
U.S. government securities	—	5,200	—	5,200
Commercial paper	—	14,122	—	14,122
Total cash equivalents	$ 1,239	$ 25,922	$ —	$ 27,161
Marketable securities				
U.S. government securities	$ —	$ 1,984	$ —	$ 1,984
Corporate bonds	—	25,475	—	25,475
Commercial paper	—	47,867	—	47,867
Total marketable securities	$ —	$ 75,326	$ —	$ 75,326
Total Assets	$ 1,239	$ 101,248	$ —	$ 102,487

	Fair Value Measurements as of December 31, 2021			
	Level 1	Level 2	Level 3	Total
Cash equivalents				
Money market funds	$ 21,085	$ —	$ —	$ 21,085
U.S. government securities	—	7,321	—	7,321
Commercial paper	—	13,198	—	13,198
Total cash equivalents	$ 21,085	$ 20,519	$ —	$ 41,604
Marketable securities				
Corporate bonds	$ —	$ 94,794	$ —	$ 94,794
Commercial paper	—	69,401	—	69,401
Total marketable securities	$ —	$ 164,195	$ —	$ 164,195
Total	$ 21,085	$ 184,714	$ —	$ 205,799

The Company classifies its money market funds as Level 1 assets since it measures fair value using quoted prices in active markets for identical assets. The Level 2 assets include commercial paper, U.S. government securities, U.S. treasuries, and corporate bonds and are valued based on quoted prices for similar assets in active markets and inputs other than quoted prices that are derived from observable market data. The Company did not hold any Level 3 assets during the periods presented.

The Company evaluates transfers between levels at the end of each reporting period. There were no transfers between Level 1 and Level 2 assets during the periods presented.

Marketable Securities

The following tables summarize the amortized cost and fair value of the Company's available-for-sale marketable debt securities (in thousands):

	December 31, 2022				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	$ 7,188	$ 1	$ (6)	$ —	$ 7,183
U.S. treasuries	6,599	1	—	—	6,600
Corporate bonds	25,656	—	(180)	—	25,476
Commercial paper	62,038	3	(52)	—	61,989
Total	$ 101,481	$ 5	$ (238)	$ —	$ 101,248

	December 31, 2021				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
Corporate bonds	$ 102,224	$ —	$ (109)	$ —	$ 102,115
Commercial paper	82,657	—	(58)	—	82,599
Total	$ 184,881	$ —	$ (167)	$ —	$ 184,714

The following table summarizes the Company's available-for-sale marketable debt securities by contractual maturity, as of December 31, 2022 and 2021 (in thousands):

	2022	2021
Maturities in one year or less	$ 98,277	$ 172,575
Maturities between one and three years	2,971	12,139
Total	$ 101,248	$ 184,714

All investments in an unrealized loss position were in this position for less than 12 months. The Company evaluated its securities for potential other-than-temporary impairment and considered the decline in market value to be primarily attributable to current economic and market conditions. Additionally, the Company does not intend to sell the securities in an unrealized loss position and does not expect it will be required to sell the securities before recovery of the unamortized cost basis. Given the Company's intent and ability to hold such securities until recovery, and the lack of a significant change in credit risk for these investments, the Company does not consider these investments to be impaired as of December 31, 2022.

There were no realized gains or losses recognized on investments for the years ended December 31, 2022 and 2021.

4. Prepaid expenses and other current assets

Prepaid expenses and other current assets consist of the following (in thousands):

	December 31,	
	2022	2021
Prepaid external research and development expenses	$ 881	$ 2,438
Inventories	3,400	2,016
Other prepayments	1,817	6,128
VAT receivable	1,077	1,169
Construction deposit - current	—	7,909
Non-trade receivables	1,851	3,351
Rent deposits	960	—
Total prepaid expenses and other current assets	$ 9,986	$ 23,011

5. Property and equipment

Property and equipment consist of the following (in thousands):

	December 31,	
	2022	2021
Property and equipment:		
Lab equipment	$ 6,722	$ 5,937
Leasehold improvements	5,069	2,450
Furniture and fixtures	226	303
Office and computer equipment	2,153	2,023
Construction-in-progress	759	211
Property and equipment	14,929	10,924
Less: accumulated depreciation	(6,791)	(6,157)
Property and equipment, net	$ 8,138	$ 4,767

Depreciation expense for the years ended December 31, 2022 and 2021 was $2.4 million and $2.2 million, respectively.

6. Intangible assets, net

Intangible assets, net of accumulated amortization, consisted of the following (in thousands):

	As of December 31, 2022		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,069	$ (509)	$ 3,560
Total	$ 4,069	$ (509)	$ 3,560

	As of December 31, 2021		
	Cost	Accumulated Amortization	Net
License milestones	$ 4,329	$ (180)	4,149
Total	$ 4,329	$ (180)	$ 4,149

License intangibles consist of capitalized milestone payments or accruals of payments the Company has deemed probable upon receiving regulatory approval of Libmeldy in the EU. The license intangibles are being amortized on a straight-line basis over the remaining useful life of the related patents of approximately twelve years. Amortization of intangible assets was $0.3 million and $0.2 million for the years ended December 31, 2022 and 2021, respectively. The effect of foreign currency translation on the net carrying value of intangible assets during the year ended December 31, 2022 was $0.2 million. The effect of foreign currency translation on the net carrying value of intangible assets during 2021 was not material.

The following table summarizes the estimated future amortization for intangible assets for the next five years and thereafter (in thousands):

2023	$ 343
2024	343
2025	343
2026	343
2027	343
Thereafter	1,845
Total	$ 3,560

7. Other assets

Other assets consist of the following (in thousands):

	December 31,	
	2022	2021
Deferred tax assets	$ 7,369	$ 4,086
Deposits	1,048	1,404
Deferred financing costs	462	693
Other non-current assets	3,196	3,407
Total other assets	$ 12,075	$ 9,590

8. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31,	
	2022	2021
Accrued external research and development expenses	$ 11,230	$ 9,273
Accrued payroll and related expenses	12,312	8,521
Accrued milestone payments	85	2,058
Accrued professional fees	2,263	854
Accrued other	2,562	2,941
Accrued governmental rebates	2,300	—
Strimvelis liability - current portion	3,685	671
Total accrued expenses and other current liabilities	$ 34,437	$ 24,318

9. Restructuring charges

On March 30, 2022, the Company announced its commitment to focus on severe neurometabolic diseases and early research programs, and to discontinue its investment in and seek strategic alternatives for the Company's programs in rare primary immune deficiencies, including OTL-103 for treatment of Wiskott Aldrich syndrome ("WAS"), OTL-102 for treatment of X-linked chronic granulomatous disease ("X-CGD"), and Strimvelis for adenosine deaminase severe combined immunodeficiency ("ADA-SCID"). During the year ended December 31, 2022, the Company recognized a one-time charge during of approximately $1.7 million, which relates to employee-related termination costs, of which $1.4 million and $0.3 million was recognized in research and development expenses and selling, general, and administrative expenses, respectively, in the Company's consolidated statements of operations and comprehensive loss. Activity during the year ended December 31, 2022, was as follows (in thousands):

	Year Ended December 31,
	2022
Balance at beginning of period	$ 6
Charged to expense	2,481
Non-cash adjustments and foreign currency translation	(760)
Payments made	(1,727)
Balance at end of period	$ -

There were no restructuring costs incurred during the year ended December 31, 2021.

10. Leases

Operating leases- office and lab space

In January 2018, December 2018, and February 2022 the Company entered into lease agreements for office space in London, United Kingdom. The leases entered into in 2018 both terminate in January 2023 and there were no options to extend the lease term. The lease entered into in March 2022 expires in February 2032 and there are no options to extend the lease term. The combined annual rental payments, including variable payments, under the lease agreements were $1.7 million in 2022 and $1.8 million in 2021. The Company also rented lab spaces in London in 2021, for which it made $0.2 million in payments in 2022 and 2021.

In March 2018, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which terminated in September 2022. The annual rental payments, including variable payments, were $0.3 million in 2022 and $0.4 million in 2021. The Company subleased the space starting in August 2021, and recognized $0.2 and $0.1 million in sublease income in 2022 and 2021, respectively.

In July 2019, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which commenced in January 2020. The lease terminates in September 2026 and has no options for term extension. The annual rental payments, including variable payments, were $1.2 million and $1.1 million in 2022 and 2021, respectively. The lease agreement includes annual rent escalation provisions.

As of December 31, 2022, the carrying value of the operating lease right-of-use assets in Boston and London was $8.1 million and the lease liabilities was $8.7 million. As of December 31, 2021, the carrying value of the operating lease right-of-use assets in Boston and London was $4.1 million and the lease liabilities was $4.3 million.

Fremont operating lease and sublease agreements

In December 2018, the Company leased manufacturing, laboratory, and office space in Fremont, California (the “Fremont facility” and the “Head Lease”) which terminates in May 2030. In May 2020, the Company committed to a restructuring plan whereby it ceased construction and build-out of the Fremont facility. In December 2020, the Company entered into a sublease agreement (the “Sublease”) with an unrelated third-party (the “subtenant”) whereby the Company subleased the entire Fremont facility to the subtenant. The Company accounts for the Head Lease and Sublease as two separate contracts. Both the Head Lease and Sublease were determined to be operating leases.

The Head Lease annual rental payments, including variable payments, were $3.2 million in 2022 and $3.1 million in 2021. The Head Lease includes annual rent escalation provisions. The Company was provided with 8 months of free rent. Subject to the terms of the Head 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 sheets.

As of December 31, 2022, the carrying value of the Fremont Head Lease right-of-use asset was $8.8 million and the lease liability was $12.0 million. The Head Lease provides for up to $5.3 million in tenant improvement allowances to be reimbursed to the Company by the landlord. These tenant improvement allowances have been included in the calculation of the operating lease liability and are currently expected to be received in 2023. The Company continues to assess the expected receipt of the tenant improvement allowances and may remeasure the right-of-use asset and liability from time to time as facts and circumstances may change.

The Sublease commenced in December 2020 and is in force for the remainder of the Head Lease term. The Sublease provided for 12 months of free rent until December 2021. The sublease provides for cash base rent payments with an annual rent escalation provision. The subtenant is also responsible for paying all operating expenses associated with the Head Lease. The Sublease also includes pass-through of up to $5.3 million in tenant improvement allowances to the subtenant, subject to the Company being reimbursed for the allowances per the terms of the Head Lease. The Subtenant provided the Company with a $2.6 million security deposit, which may be converted to a letter of credit upon providing evidence of $2.6 million in construction expenditures. The Company accounts for the security deposit within other long-term liabilities.

Embedded operating lease arrangement

In July 2020, the Company entered into a manufacturing and technology development master agreement for research and development and commercial production with AGC Biologics, S.p.A. (formerly MolMed S.p.A.) (“AGC”) pursuant to which AGC will develop, manufacture and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs ("AGC Agreement").

The Company determined that the AGC Agreement contains an embedded lease as it includes a provision for manufacturing suites designated for the Company's exclusive use during the term of the agreement. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The Company does not deem it probable that it will exercise the option to extend as of December 31, 2022. The Company paid $2.5 million and $3.1 million in rental payments in 2022 and 2021, respectively. As of December 31, 2022, the carrying value of the embedded operating lease right-of-use asset was $5.8 million and the lease liability was $5.3 million. As of December 31, 2021, the carrying value of the embedded operating lease right-of-use asset was $10.7 million and the lease liability was $9.3 million.

Summary of all lease costs recognized under ASC 842

Our facility leases described above generally contain customary provisions allowing the landlords to terminate the leases if we fail to remedy a breach of any of our obligations under any such lease within specified time periods, or upon our bankruptcy or insolvency. The leases do not include any restrictions or covenants that had to be accounted for under the lease guidance. The following table contains a summary of the lease-related costs recognized within operating expenses, and other information pertaining to the Company's operating leases as of December 31, 2022 and 2021 (in thousands, where applicable):

	2022	2021
Fixed lease cost	$ 7,693	$ 7,701
Variable lease cost	1,602	1,696
Sublease income	(2,820)	(2,746)
Total lease cost	$ 6,475	$ 6,651
Other information		
Operating cash flows used for operating leases	$ 7,442	$ 7,989
Weighted-average remaining lease term (years)	6.5	6.0
Weighted-average discount rate	8.5%	8.7%

Fixed lease cost represents the ASC 842 rent expense associated with the amortization of our right-of-use assets and lease liabilities. Variable lease cost are the amounts owed by the Company to a lessor that are not fixed, such as reimbursement for common area maintenance and utilities costs and are not included in the calculation of the Company's operating lease right of use assets or operating lease liabilities and are expensed when incurred. Sublease income represents the straight-line recognition of base rent sublease income over the term of the Sublease, and recognition of pass-through operating expense costs per the terms of the Sublease.

During the year ended December 31, 2022, the Company obtained right of use assets valued at $6.1 million in exchange for lease liabilities of $6.1 million. During the year ended December 31, 2021, the Company obtained $0.6 million in right of use assets in exchange for $0.6 million in lease liabilities.

As of December 31, 2022, future minimum base rent commitments under ASC 842 under the Company's property leases were as follows (in thousands):

Due in:	Gross lease payments	Gross sublease receipts	Net lease payments
2023	$ 6,517	$ (2,246)	$ 4,271
2024	6,972	(2,313)	4,659
2025	6,035	(2,382)	3,653
2026	4,809	(2,454)	2,355
2027	3,774	(2,527)	1,247
Thereafter	12,266	(6,432)	5,834
Total future minimum lease payments	$ 40,373	$ (18,354)	$ 22,019
Less: imputed interest	(14,703)		
Total operating lease payments	$ 25,670		

11. Notes payable

In May 2019, the Company entered into a senior term facilities agreement, which was amended in April 2020 (the "Original Credit Facility") with MidCap Financial (Ireland) Limited ("MidCap Financial"), as agent, and additional lenders from time to time (together with MidCap Financial, the "Lenders"), to borrow up to $75.0 million in term loans.

In May 2021, the Company amended and restated the Original Credit Facility (the "Amended Credit Facility"). Under the Amended Credit Facility, the Lenders agreed to make term loans available to the Company in the aggregate amount of $100.0 million, including increasing the principal on the initial term loan to $33.0 million, from $25.0 million. To date, the Company has borrowed $33.0 million under the amended initial term loan. The remaining $67.0 million under the Amended Credit Facility may be drawn down in the form of a second and third term loan, the second term loan being a $33.0 million term loan available no earlier than July 1, 2022 and no later than July 1, 2023 upon certain regulatory approvals and evidence of the Company having $100 million in cash and cash equivalent investments; and the third term loan being a $34.0 million term loan available no earlier than July 1, 2023 and no later than July 1, 2024 upon evidence of the Company having $100 million in cash and cash equivalent investments and attaining a pre-specified trailing 12-month revenue target.

Each term loan under the Amended Credit Facility bears interest at an annual rate equal to 5.95% plus LIBOR. The Company is required to make interest-only payments on the term loan for 18 months following the date of the Amended Credit Facility, unless the Company is eligible for the second tranche, in which case the Company may elect to make interest-only payments for 30 months following the date of the Amended Credit Facility. The term loans under to the Amended Credit Facility begin amortizing on either the 18-month or the 30-month anniversary of the Amended Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by the Company to the Lenders in consecutive monthly installments until the loan maturity date. In addition, a final payment of 3.5% is due on the loan maturity date. The Company is accruing the final payment amount of $1.2 million associated with the first term loan of the Amended Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the loan maturity date.

The Amended Credit Facility includes affirmative and negative covenants. The affirmative covenants include, among others, covenants requiring the Company to maintain their legal existence and governmental approvals, deliver certain financial reports, maintain insurance coverage, maintain property, pay taxes, satisfy certain requirements regarding accounts and comply with laws and regulations. The negative covenants include, among others, restrictions on the Company transferring collateral, incurring additional indebtedness, engaging in mergers or acquisitions, paying dividends or making other distributions, making investments, creating liens, amending material agreements and organizational documents, selling assets, changing the nature of the business and undergoing a change in control, in some cases subject to certain exceptions. The Company is also subject to an ongoing minimum cash financial covenant in which the Company must maintain unrestricted cash in an amount not less than $20.0 million following the utilization of the second term loan and not less than $35.0 million following the utilization of the third term loan.

In January 2023, the Company again amended and restated the credit facility to change from LIBOR to SOFR. The newly amended facility bears a variable interest rate of 5.95% above SOFR plus 0.10% per annum, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility.

Notes payable consisted of the following (in thousands):

	December 31,	
	2022	2021
Notes payable, net of issuance costs	$ 31,970	$ 32,669
Less: current portion	(9,429)	(786)
Notes payable, net of current portion	22,541	31,883
Accretion related to final payment	450	203
Notes payable, long term	$ 22,991	$ 32,086

As of December 31, 2022, the future principal payments and final payment that are due are as follows (in thousands):

	Aggregate Minimum Payments
2023	$ 9,429
2024	9,429
2025	9,429
2026	5,084
Total	33,371
Less current portion	(9,429)
Less unamortized portion of final payment	(705)
Less unamortized debt issuance costs	(246)
Notes payable, long term	$ 22,991

During the years ended December 31, 2022 and 2021, the Company recognized $3.0 million and $2.5 million of interest expense related to the term loan, respectively. The effective annual interest rate as of December 31, 2022 and 2021, on the outstanding debt under the Term Loan was approximately 9.2% and 8.4%, respectively.

12. Share-based compensation

The Company maintains four equity compensation plans; the Orchard Therapeutics Limited Employee Share Option Plan with Non-Employee Sub-Plan and U.S. Sub-Plan (the "2016 Plan"), the Orchard Therapeutics plc 2018 Share Option and Incentive Plan (the "2018 Plan"), the 2018 Employee Share Purchase Plan (the "ESPP"), and the 2020 Inducement Equity Plan (the "Inducement Plan"). The board of directors has determined not to make any further awards under the 2016 plan. As of December 31, 2022, there were 5,341,768 shares available for grant under the 2018 Plan, 721,500 available for grant under the Inducement Plan, and 627,677 shares available for grant under the ESPP.

The numbers of options and restricted stock units, the weighted average grant date fair values per stock option and per share, and the weighted average exercise prices are all shown below on a per ordinary share basis. Effective March 10, 2023, The Company's ADSs that are listed on the NASDAQ Capital Market each represent ten ordinary shares.

On October 4, 2022, the Company's Compensation Committee approved a one-time stock option repricing for certain previously granted and still outstanding options held by the Company's employees and certain independent contractors which had an exercise price above $1.25. As a result of the repricing, the exercise price for 7,946,139 vested and unvested options outstanding was lowered to $0.58. No other terms of the repriced options were modified and the repriced stock will continue to vest according to their original vesting schedules and will retain their original expiration dates. The repricing resulted in one-time stock-based compensation expense of $0.9 million related to vested options and incremental stock option expense of $0.8 million related to unvested options which will be amortized on a straight-line basis over the remaining vesting period of those options.

Share options

The fair value of each stock option award is estimated on the date of grant using the Black-Scholes option-pricing model using the range of assumptions for the years ended December 31, 2022 and 2021, as noted in the following table:

	Year Ended December 31,	
	2022	2021
Risk-free interest rate	1.5% - 4.4%	0.5% - 1.3%
Expected term (in years)	2.0 - 6.1	5.3 - 6.1
Expected volatility	74.4% - 79.5%	74.2% - 78.7%
Expected dividend rate	0.0%	0.0%

The following table summarizes option activity under the plans for the year ended December 31, 2022:

	Shares	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2021	17,300,740	$ 6.57		
Granted	4,600,154	0.56		
Exercised	(699,234)	-		
Forfeited	(4,777,493)	6.81		
Outstanding at December 31, 2022	16,424,167	$ 1.56	7.38	$ -
Vested and expected to vest at December 31, 2022	16,424,167	$ 1.56	7.38	$ -
Exercisable at of December 31, 2022	9,212,552	$ 2.28	6.26	$ -

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 the years ended December 31, 2022 and 2021, the total intrinsic value of share options exercised was $0.4 million and $7.4 million, respectively. The weighted average grant date fair value per share of options granted during the years ended December 31, 2022 and 2021, was $0.32 and $3.10, respectively.

Restricted share units

CEO award

The Company granted 195,000 performance based RSUs with a total grant date fair value of $1.4 million to its Chief Executive Officer, Bobby Gaspar, M.D., Ph.D., in April 2020. The award vests on January 2, 2024 as to 1/3 of the award for each of the first three to occur of four milestones, if each such milestone is achieved by the Company on or before December 31, 2023 and Dr. Gaspar remains continuously employed with the Company through January 2, 2024. The milestones relate to the achievement of specific clinical and regulatory milestones. No performance-based share unit performance conditions associated with the CEO award were deemed probable and none vested during the year ended December 31, 2022.

Time-based restricted share units

Time-based restricted share units vest in equal annual installments over a three-year period.

The following table summarizes restricted share unit award activity for the year-end December 31, 2022:

	Performance-based RSUs	Time-based RSUs	Total RSUs	Weighted Average Grant Date Fair Value per Share
Unvested at December 31, 2021	195,000	123,333	318,333	$ 6.41
Granted	—	2,192,988	2,192,988	0.46
Vested	—	(55,001)	(55,001)	5.58
Forfeited	—	(392,444)	(392,444)	0.60
Unvested at December 31, 2022	195,000	1,868,876	2,063,876	$ 0.55

During the years ended December 31, 2022 and 2021, the total fair value of time-based RSU's that vested was $0.3 million and $0.3 million, 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 (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development	$ 6,791	$ 9,214
Selling, general and administrative	9,219	13,322
Total	$ 16,010	$ 22,536

Total share-based compensation by award type was as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Restricted share units	$ 838	$ 550
Share options	15,172	21,986
Total	$ 16,010	$ 22,536

As of December 31, 2022, total unrecognized compensation cost related to options was $14.0 million. This amount is expected to be recognized over a weighted average period of 2.34 years. As of December 31, 2022, total unrecognized compensation cost related to time-based RSUs was $0.8 million. This amount is expected to be recognized over a weighted average period of 1.96 years. As of December 31, 2022, the total unrecognized compensation cost related to performance-based RSUs is a maximum of $1.4 million, the timing of recognition will be dependent upon achievement of milestones.

13. License and research arrangements

GSK asset purchase and license agreement

In April 2018, the Company completed 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 pre-clinical development from Telethon Foundation and San Raffaele Hospital ("Telethon-OSR"). The portfolio of programs and options acquired consisted of two late-stage clinical gene therapy programs in ongoing registrational trials for MLD and WAS, one earlier stage clinical gene therapy program for TDT, Strimvelis, and option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which option rights have all subsequently lapsed.

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, resulting in total consideration of $133.6 million, which was recorded in the second quarter of 2018.

The Company is required to use commercially reasonable efforts to obtain a Priority Review Voucher ("PRV") from the United States Food and Drug Administration for each of the programs for MLD, WAS and TDT, the first of which GSK retained beneficial ownership over. 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 TDT. If GSK does not exercise this option to purchase any PRV, the Company may sell the PRV to a third party and must share any proceeds in excess of a specified sale price equally with GSK. As part of the GSK Agreement the Company is also required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy 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.

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. The Company will pay a flat mid-single digit percentage royalty on the annual net sales of Strimvelis. 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 a percentage from the high single-digits to low double-digit for the TDT product, upon marketing approval, calculated as percentages of aggregate annual net sales of the TDT 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 or through December 31, 2022, and are not included as part of consideration.

Telethon-OSR research and development collaboration and license agreements

In connection with the Company's entering into the GSK Agreement in April 2018, 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 and TDT.

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones, up to an aggregate of approximately €31.0 million ($33.4 million at December 31, 2022). 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.

In May 2019, the Company entered into a license agreement with Telethon-OSR, under which Telethon-OSR granted to the Company an exclusive worldwide license for the research, development, manufacture and commercialization of Telethon-OSR's ex vivo autologous HSC lentiviral based gene therapy for the treatment of mucopolysaccharidosis type I, including the Hurler variant ("MPS-IH"). Under the terms of the agreement, Telethon-OSR received €15.0 million ($16.1 million at December 31, 2022) in upfront and milestone payments from the Company upon entering into the agreement, resulting in $17.2 million in in-process research and development expense. The Company is also required to pay up to €28.0 million ($30.1 million at December 31, 2022) related to milestone payments contingent upon achievement of certain development, regulatory and commercial milestones. Additionally, the Company will be required to pay Telethon a tiered mid-single to low-double digit royalty percentage on annual net sales of licensed products.

UCLB/UCLA license agreement

In February 2016, and amended in July 2017, the Company completed 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 expenses based on the fair value of the ordinary shares as of the time the agreement was executed or modified.

Under the UCLB/UCLA License Agreement, the Company may become obligated to make payments to the parties of up to an aggregate of £19.9 million ($24.1 million at December 31, 2022) 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 June 2021, the Company terminated the license to its OTL-101 program for ADA-SCID, which was granted pursuant to the UCLB/UCLA license agreement. Except for the termination of such license, the UCLB/UCLA license agreement continues in full force and effect. 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 June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica plc whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and whereby Oxford BioMedica will provide process development services ("Oxford BioMedica Development Agreement"). As part of the consideration to rights and licenses granted under the Oxford BioMedica Development 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 another 150,826 ordinary shares, and issued these shares in 2018. In September 2018, the second and fourth milestones were achieved, and the Company issued 150,826 ordinary shares. In April 2020, the fifth milestone was deemed to have been met upon execution of the amended agreement in April 2020, and the Company issued another 75,413 ordinary shares to Oxford BioMedica with a total value of $0.8 million which was recorded to research and development expense. No milestones were met during the year ended December 31, 2022. The Company may also pay low single-digit percentage royalties on net sales of collaborated products generated under the Oxford BioMedica Agreement.

14. Income taxes

The components of net loss before income taxes for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	December 31,	
	2022	2021
U.K.	$ (156,000)	$ (147,337)
Non-U.K.	2,966	3,581
Net loss before taxes	$ (153,034)	$ (143,756)

The provision for (benefit from) income taxes for the years ended December 31, 2022 and 2021 are as follows (in thousands):

	December 31,	
	2022	2021
Current (benefit) provision		
Federal—United States	$ 618	$ (1,025)
State—United States	144	334
Other foreign	147	388
United Kingdom	—	—
Total current (benefit) provision	909	(303)
Deferred provision (benefit)		
Federal—United States	(3,066)	1,099
State—United States	(204)	(312)
United Kingdom	(13)	—
Other foreign	—	344
Total deferred provision (benefit)	(3,283)	1,131
Total provision (benefit) for income taxes	$ (2,374)	$ 828

The following table presents a reconciliation of income tax expense (benefit) computed at the UK statutory income tax rate to the effective income tax rate as reflected in the consolidated financial statements (in thousands):

	December 31,	
	2022	2021
Income taxes at United Kingdom statutory rate	$ (29,072)	$ (27,313)
Change in valuation allowance	34,333	59,691
Reduction in research expense for credits granted	1,805	6,674
Change in tax rates	(8,240)	(38,785)
Tax credits	(2,049)	(2,232)
U.S. Deduction for foreign derived intangible income	(1,489)	(196)
Permanent differences, including share-based compensation deduction shortfalls	2,387	2,863
U.S. state income taxes	(45)	17
Foreign rate differential	(4)	109
Total provision (benefit) for income taxes	$ (2,374)	$ 828

The Company's income tax expense for the year ended December 31, 2022, compared to the year ended December 31, 2021, decreased primarily related to an increase of the U.S. deduction for foreign derived intangible income ("FDII"), a decrease to the amount of shortfalls related to share-based compensation that is not deductible for tax purposes, and a decrease in the non-U.K. profit before tax.

During 2021, the U.K. Government announced that from April 1, 2023, the corporation tax rate would increase to 25%. This new law was enacted on June 10, 2021. The overall effect of the change was an increase in net deferred tax assets of $38.8 million and an increase in valuation allowance by an equal amount.

The Company accounts for income taxes in accordance with ASC Topic 740. Deferred income tax assets and liabilities are determined based upon temporary differences between the financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The following table presents the principal components of the Company's deferred tax assets and liabilities as of December 31, 2022 and 2021 (in thousands):

	December 31,	
	2022	2021
Deferred tax assets		
Net operating loss carryforwards	$ 158,344	$ 126,563
Amortization	11,215	25,206
Research and development credits	2,525	2,449
Capitalized research and development costs	2,285	—
Share-based compensation	9,282	9,353
Accruals	946	798
Lease liability	6,126	6,444
Property and equipment	—	1,022
Total deferred tax assets	190,723	171,835
Valuation allowance	(177,630)	(161,573)
Fixed assets and right-of-use asset	(5,724)	(6,176)
Other non-current assets (net deferred tax assets and liabilities)	$ 7,369	$ 4,086

For the years ended December 31, 2022 and 2021, the Company had cumulative U.K. net operating loss carryforwards of approximately $633.4 million and $506.2 million, respectively. U.K. losses not surrendered may be carried forward indefinitely, subject to numerous utilization criteria and restrictions and are fully offset by a valuation allowance. For the years ended December 31, 2022 and 2021, the Company also had U.S. federal orphan drug tax credits of $0.7 million and $0.6 million, respectively, and U.S. state research and development tax credits of $2.2 million and $2.4 million. The U.S. federal orphan drug tax credits expire in 2042, while the U.S. state research and development credits may be carried forward indefinitely and are offset by a valuation allowance.

In measuring the Company's deferred tax assets, the Company considers all available evidence, both positive and negative, to determine whether, based on the weight of that evidence, a valuation allowance is needed for all or some portion of the deferred tax assets. Significant judgment is required in considering the relative impact of the negative and positive evidence, and weight given to each category of evidence is commensurate with the extent to which it can be objectively verified. The more negative evidence that exists, the more positive evidence is necessary, and the more difficult it is to support a conclusion that a valuation allowance is not needed. Additionally, the Company utilizes the "more likely than not" criteria established in FASB ASC Topic 740 to determine whether the future tax benefit from the deferred tax assets should be recognized. As a result, the Company has established valuation allowances on the deferred tax assets in jurisdictions that have incurred net operating losses and in which it is more likely than not that such losses will not be utilized in the foreseeable future.

As of each reporting date, the Company considers new evidence, both positive and negative, that could impact the Company's view with regard to the future realization of our deferred tax assets. Management has considered the Company's history of cumulative net losses in the U.K., along with estimated future taxable income and has concluded that it is more likely than not that the Company will not realize the benefits of its U.K. deferred tax assets and U.S. state research and development tax credits. Accordingly, the Company has maintained a full valuation allowance against these net deferred tax assets as of December 31, 2022 and 2021, respectively.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2022 and 2021 related primarily to the increase in UK net operating loss carryforwards as follows (in thousands):

	December 31,	
	2022	2021
Valuation allowance as of beginning of year	$ (161,573)	$ (103,890)
Increases recorded to income tax provision	(34,248)	(59,691)
Effect of foreign currency translation	18,191	2,008
Valuation allowance as of end of year	$ (177,630)	$ (161,573)

The Company applies the authoritative guidance on accounting for and disclosure of uncertainty in tax positions, which requires the Company to determine whether a tax position of the Company is more likely than not to be sustained upon

examination, including resolution of any related appeals of litigation processes, based on the technical merits of the position. For tax positions meeting the more likely than not threshold, the tax amount recognized in the financial statements is reduced by the largest benefit that has a greater than fifty percent likelihood of being realized upon the ultimate settlement with the relevant taxing authority. There were no material uncertain tax positions as of December 31, 2022 and 2021.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2022, and 2021, the Company had no accrued interest or penalties related to uncertain tax positions and no amounts have been recognized in the Company's statement of operations.

The Company and its subsidiaries file income tax returns in the UK, the U.S., and various foreign jurisdictions. Generally, the tax years 2018 through 2022 remain open to examination by the major taxing jurisdictions to which the Company is subject. To the extent the Company has tax attribute carryforwards, the tax years in which the attribute was generated may still be adjusted upon examination by the federal, state, or foreign tax authorities, if such tax attributes are utilized in a future period.

15. Product revenue, net

The following table presents the Company's net revenue by product (in thousands):

	Year Ended December 31,	
	2022	2021
Libmeldy	$ 18,796	$ —
Strimvelis	1,814	700
Total	$ 20,610	$ 700

Net product revenue of Libmeldy by geography consisted of the following and is attributable to individual countries based on the location of the customer as of December 31, 2022 (in thousands):

	Year ended December 31, 2022
United Kingdom	$ 6,322
Italy	5,544
France	3,883
Germany	3,047
Total Libmeldy revenue, net	$ 18,796

As of December 31, 2022 and 2021, all Strimvelis revenue was generated in Italy.

Activity in each of the product revenue allowance and reserve categories for Libmeldy is summarized as follows (in thousands):

	Trade Discounts and Allowances	Government rebates	Total
Balance as of December 31, 2021	$ —	$ —	$ —
Provision Related to sales in the current year	4,573	2,300	6,873
Credits and payments made during the period	(183)	—	(183)
Balance as of December 31, 2022	$ 4,390	$ 2,300	$ 6,690

The total reserves described above are summarized as components of the Company's consolidated balance sheets as follows (in thousands):

	December 31, 2022
Reduction of accounts receivable, net	$ 4,390
Component of accrued expenses and other current liabilities	2,300
Balance as of December 31, 2022	$ 6,690

There were no Libmeldy reserves or revenue allowances as of December 31, 2021. Strimvelis had no trade discounts and allowances or government rebates in the years ended December 31, 2022 and 2021.

16. Collaboration revenue

On July 1, 2021, the Company entered into a strategic collaboration with Pharming Group N.V. ("Pharming") to research, develop, manufacture, and commercialize OTL-105, an investigational *ex vivo* autologous HSC gene therapy for the treatment of hereditary angioedema (HAE), a life-threatening rare disorder that causes recurring swelling attacks in the face, throat, extremities and abdomen (the "Collaboration Agreement").

Under the terms of the Collaboration Agreement, Pharming was granted worldwide rights to OTL-105 and will be responsible for clinical development, regulatory filings and commercialization of the investigational gene therapy, including associated costs. The Company will lead the completion of IND-enabling activities and oversee manufacturing of OTL-105 during pre-clinical and clinical development, which will be funded by Pharming. In addition, both the Company and Pharming will explore the application of non-toxic conditioning regimen for use with OTL-105 administration.

The Company received an upfront payment of $10.0 million in cash from Pharming. The Company is also eligible to receive up to $189.5 million in development, regulatory and sales milestones as well as mid-single to low double-digit percentage royalty payments on future worldwide sales.

The Company also entered into a Share Purchase Agreement with Pharming on July 1, 2021 (the "SPA"), pursuant to which the Company issued 1,227,738 ordinary shares to Pharming for total consideration of $7.5 million. The consideration is payment for the fair value of ordinary shares with a fair value of $4.1 million plus a $3.4 million premium on the fair value of the Company's ordinary shares. The "Collaboration Agreement" and the "SPA" are referred to together as the "Pharming Agreements."

Accounting analysis

At the commencement of the arrangement, two units of accounting were identified, which are the issuance of 1,227,738 of the Company's ordinary shares as part of the SPA, and the license and collaboration agreement, which conveys the license and provides for the Company to provide research, development, manufacturing services for OTL-105. The Pharming Agreements were entered into concurrently as part of a single commercial objective and the Company considers them a single arrangement for accounting purposes. The total upfront payments of $17.5 million are comprised of $4.1 million attributed to the equity sold to Pharming and $13.4 million attributed to the Collaboration Agreement.

The Company has concluded that the conveyance of the license for the HAE program and the provision of research, development, and manufacturing services for the HAE program represent a series of distinct services that are accounted for as a single performance obligation within the Collaboration Agreement.

The Company determined that the transaction price includes: the $13.4 million attributed to the Collaboration Agreement and the variable consideration for estimated reimbursement payments at agreed upon contractual rates to be received from Pharming for the Company's on-going research, development, and manufacturing services. The potential future variable consideration is associated with the reimbursement for research, development, and manufacturing services provided by the Company to Pharming at agreed upon contractual rates which is the only remaining unsatisfied performance obligation. The milestone payments included in the Collaboration Agreement are fully constrained as a result of the uncertainty regarding whether any of the associated milestones will be achieved. The Company re-evaluates the transaction price as of the end of each reporting period.

The Company recognizes revenue associated with the performance obligation as the research, development, and manufacturing services are provided using an input method, based on the cumulative costs incurred compared to the total estimated costs expected to be incurred to satisfy the performance obligation. The transfer of control to the customer occurs over the time period that the research, development and manufacturing services are to be provided by the Company. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred consistent with the cost-to-cost method. The estimated costs associated with the remaining efforts required to complete the performance obligations may change which may materially impact revenue recognition and the Company regularly evaluates and, when necessary, updates the costs associated with the remaining efforts. Accordingly, revenue may fluctuate from period to period due to revisions to estimated costs resulting in a change in the measure of progress for the performance obligation or if the transaction price changes due to inclusion of any milestone payments that become unconstrained.

The following table summarizes research and development costs incurred and collaboration revenue recognized in connection with the Company's performance under the Collaboration Agreement (in thousands):

	Year Ended December 31,	
	2022	2021
Reimbursement revenue	$ 1,776	$ 843
Upfront and milestone payment revenue	269	132
Total	$ 2,045	$ 975

The Company had $0.5 million and $0.8 due from Pharming included in accounts receivable as of December 31, 2022 and 2021, respectively.

As of December 31, 2022, the Company had contract liabilities of $11.3 million, of which $1.0 million was classified as current and $10.3 million was classified as long-term in the consolidated balance sheets. The deferred revenue balance represents the portion of the upfront payments received related to the performance obligation that remains partially unsatisfied as of December 31, 2022.

17. Commitments and contingencies

Lease commitments

The Company leases office and laboratory space and has an embedded lease with AGC. Refer to Note 10 for further information on the terms of our lease agreements.

Manufacturing and technology development master agreement with AGC

On July 2, 2020, the Company entered into the AGC Agreement pursuant to which AGC will develop, manufacture, and supply certain viral vectors and conduct cell processing activities for certain Company development and commercial programs. Under the terms of the AGC Agreement, the Company is obligated to pay AGC for a minimum product manufacturing commitment, dedicated manufacturing and development resources, and for a lease component associated with the right of use of exclusive manufacturing suites within AGC's existing facilities. The following table outlines the annual commitments associated with the contract as of December 31, 2022 (in thousands):

Due in:	Product manufacturing commitments (1)	Dedicated manufacturing and development resources (2)	Exclusive transduction suites (3)	Total AGC Commitment
2023	$ 1,933	$ 5,655	$ 2,147	$ 9,735
2024	1,933	5,655	2,147	9,735
2025	966	2,827	1,074	4,867
Total manufacturing commitments	$ 4,832	$ 14,137	$ 5,368	$ 24,337

The tabular disclosure above has been translated from Euros to U.S. Dollars using an exchange rate of €1.00 to $1.07.

(1) The minimum product manufacturing commitments may be increased to the mid-seven figures per contract year upon achievement of certain milestones.

(2) The Company may increase or decrease the usage of dedicated development services on a rolling basis with between six and 12-months' prior written notice to AGC. The above table assumes continued usage of dedicated development services at current rates.

(3) Refer to Note 10 for further information on the embedded operating lease agreement

The Company incurred $13.7 million and $16.4 million in expenses related to the AGC Agreement in the years ended December 31, 2022 and 2021, respectively. The AGC Agreement has an initial term of five years, beginning on the Effective Date and ending July 2, 2025. The AGC Agreement may be extended for an additional two years by mutual agreement of the Company and AGC. The Company has the right to terminate the AGC Agreement at its discretion upon 12-month's prior written notice to AGC, and beginning no earlier than July 2, 2022, AGC has the right to terminate the AGC Agreement at its discretion upon 24-month's prior written notice to the Company. Each party may terminate the AGC Agreement upon prior notice to the other party for an uncured material breach that the breaching party does not cure within the notice period.

Other funding commitments

The Company has entered into several license agreements (see Note 13). In connection with these agreements the Company is required to make milestone payments and annual license maintenance payments or royalties on future sales of specified products.

Legal proceedings

The Company is not a party to any litigation and does not have contingency reserves established for any litigation liabilities.

Indemnification agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners, and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of its board of directors and senior management that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company is not aware of any claims under indemnification arrangements, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2022 or 2021.

18. 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 six percent of each employee's annual salary based on the jurisdiction in which the employees are located. The Company paid $1.6 million and $1.7 million, in matching contributions for the years ended December 31, 2022 and 2021, respectively.

19. Subsequent events

Ratio change

On February 10, 2023, the Company announced that the Company's Board of Directors approved a change to the ratio of the Company's ADSs to ordinary shares (the "ADS Ratio") from the previous ADS Ratio of one ADS to one ordinary share to a new ADS Ratio of one ADS to ten ordinary shares. The ratio change became effective on March 10, 2023. The change in the ADS Ratio had the same effect as a one-for-ten reverse ADS split and is intended to enable the Company to regain compliance with the Nasdaq minimum bid price requirement. As all financial statement and disclosure information is presented in ordinary share amounts, not ADSs, there was no impact to the consolidated financial statements and footnote disclosures.

Issuance of shares through 2023 Private Placement

On March 6, 2023, the Company entered into a Securities Purchase Agreement (the "Purchase Agreement") pursuant to which the Company agreed to sell, in an unregistered offering, up to an aggregate of (i) 99,166,900 shares, consisting of a combination of Ordinary Shares, nominal value £0.10 per share ("Ordinary Shares") and Non-Voting Ordinary Shares, nominal value £0.10 per share ("Non-Voting Ordinary Shares" and together with the Ordinary Shares, "Shares") and (ii) warrants to purchase an aggregate of 109,083,590 Ordinary Shares or Non-Voting Ordinary Shares (the "Warrants").

The 2023 Private Placement consists of two closings. The Company agreed to sell and issue in the initial closing of the 2023 Private Placement (i) 56,666,900 Shares and (ii) Warrants to purchase an aggregate of 62,333,590 Shares, at a purchase price of $6.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The initial closing of the 2023 Private Placement occurred on March 10, 2023. The Company received gross proceeds of approximately $34.0 million from the initial closing of the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Company.

In addition, the Company agreed to sell and issue in the second closing of the 2023 Private Placement (i) 42,500,000 Shares and (ii) Warrants to purchase an aggregate of 46,750,000 Shares, at a purchase price of $8.00 per unit, where each unit consists of ten (10) Shares and an accompanying Warrant to purchase eleven (11) Shares. The second closing is conditioned upon (x) the Company's announcement of its intention to file a biologics license application ("BLA") submission following receipt of the minutes from the U.S. Food and Drug Administration ("FDA") in connection with the Company's pre-BLA (Type B) meeting for OTL-200, provided such minutes do not expressly advise the Company not to proceed with a BLA submission, and (y) receipt of Shareholder Approval (as defined below) (collectively, the "Second Closing Trigger").

In connection with the Private Placement, the Company has agreed to hold a meeting of its shareholders no later than 120 days following the initial closing of the Private Placement to seek approval to give the Company's directors authority under s551 Companies Act 2006 to issue the securities to be issued and sold in the second closing of the Private Placement and the Shares issuable upon exercise of the Warrants to be issued and sold in the Private Placement, and to disapply pre-emption rights in respect of such authority under s570 of the Companies Act 2006 (collectively, "Shareholder Approval").

The second closing is expected to occur on the fifth trading day after the Company notifies the purchasing parties that the Second Closing Trigger has occurred and is subject to additional, customary closing conditions. If the Second Closing Trigger occurs, the Company anticipates receiving gross proceeds of approximately $34.0 million from the second closing of

the 2023 Private Placement, before deducting fees to the placement agent and other offering expenses payable by the Company.

Each Warrant will have an exercise price equal to $1.10 per Share in the event the Vesting Event (as defined below) occurs on or prior to December 31, 2024, and $0.95 per Share in the event the Vesting Event occurs after December 31, 2024. The Warrants will be exercisable during the 30 days following the Company's announcement of receipt of marketing approval of its BLA with respect to OTL-200 (the "Vesting Event"); provided that exercise of any Warrant is conditioned upon the receipt of Shareholder Approval. Commencement of the 30-day exercise period may be delayed as set forth in the Warrants in the event the Vesting Event occurs prior to Shareholder Approval. The Warrants will expire at the conclusion of the 30-day exercise period or, if the Vesting Event does not occur, March 10, 2026.

ORCHARD THERAPEUTICS PLC

and

CITIBANK, N.A.,

as Depositary,

and

THE HOLDERS AND BENEFICIAL OWNERS OF
AMERICAN DEPOSITARY SHARES
OUTSTANDING UNDER THE TERMS OF THE
DEPOSIT AGREEMENT, DATED AS OF NOVEMBER 2, 2018

Amendment No. 1
to
the Deposit Agreement

Dated as of March 10, 2023

AMENDMENT NO. 1 TO THE DEPOSIT AGREEMENT

AMENDMENT NO. 1 TO THE DEPOSIT AGREEMENT, dated as of March 10, 2023 ("Amendment No. 1"), by and among Orchard Therapeutics plc, a public limited company incorporated under the laws of England and Wales, and its successors (the "Company"), Citibank, N.A., a national banking association organized under the laws of the United States of America (the "Depositary"), and all Holders and Beneficial Owners of American Depositary Shares issued and outstanding as of the date hereof pursuant to the Deposit Agreement (as hereinafter defined).

WITNESSETH THAT:

WHEREAS, the Company and the Depositary entered into that certain Deposit Agreement, dated as of November 2, 2018 (as so amended and supplemented from time to time, the "Deposit Agreement"), for the creation of ADSs (as defined in the Deposit Agreement) representing the Shares (as defined in the Deposit Agreement) deposited thereunder and for the execution and delivery of American Depositary Receipts ("ADRs") in respect of the ADSs; and

WHEREAS, the Company desires to (a) change the ADS-to-Share ratio from (i) the existing ratio of one (1) ADS to one (1) Share to (ii) a new ratio of one (1) ADS to ten (10) Shares, (b) amend the Deposit Agreement, the ADRs currently outstanding, and the form of ADR annexed as Exhibit A to the Deposit Agreement, in each case pursuant to Section 6.1 of the Deposit Agreement, to reflect such changes, and (c) give notice thereof to all Holders (as defined in the Deposit Agreement) of ADSs.

NOW, THEREFORE, for good and valuable consideration, the receipt and sufficiency of which are hereby acknowledged, the Company and the Depositary hereby agree to amend the Deposit Agreement, the ADRs currently outstanding, and the form of ADR annexed as Exhibit A to the Deposit Agreement as follows:

ARTICLE I

DEFINITIONS

Section 1.1 Definitions. Unless otherwise specified in this Amendment No. 1, all capitalized terms used, but not defined, herein shall have the meanings ascribed to such terms in the Deposit Agreement.

Section 1.2 Effective Date. The term "Effective Date" shall mean the date set forth above and as of which this Amendment No. 1 shall become effective.

ARTICLE II

AMENDMENTS TO DEPOSIT AGREEMENT

Section 2.1 Deposit Agreement. All references in the Deposit Agreement to the term "Deposit Agreement" shall, as of the Effective Date, refer to the Deposit Agreement, dated as of November 2, 2018, and as amended by this Amendment No. 1, and as further amended and supplemented after the Effective Date.

Section 2.2 Amendments Binding on all Holders and Beneficial Owners. From and after the Effective Date, the amendments to the Deposit Agreement, the ADRs currently outstanding, and the form of ADR annexed as Exhibit A to the Deposit Agreement effected hereby shall be binding on all Holders and Beneficial Owners of ADSs issued and outstanding as of the Effective Date and on all Holders and Beneficial Owners of ADSs issued after the Effective Date.

ARTICLE III

AMENDMENTS TO THE FORM OF ADR

Section 3.1 ADR Amendments.

(a) The phrase in the top, right-hand corner of the Form of ADR attached as Exhibit A to the Deposit Agreement and in each of the ADRs issued and outstanding under the

terms of the Deposit Agreement is hereby amended as of the Effective Date by deleting such phrase in its entirety and inserting the following in its stead:

> "American Depositary Shares (each American Depositary Share representing the right to receive ten (10) fully paid ordinary shares)"

(b) The second sentence of the introductory paragraph of the Form of ADR attached as Exhibit A to the Deposit Agreement and in each of the ADRs issued and outstanding under the terms of the Deposit Agreement is hereby amended as of the Effective Date by deleting such sentence in its entirety and inserting the following in its stead:

> "As of the date of issuance of this ADR, each ADS represents the right to receive ten (10) Shares deposited under the Deposit Agreement (as hereinafter defined) with the Custodian, which at the date of the execution of the Deposit Agreement was Citibank, N.A. (London) (the "Custodian")."

(c) The first sentence of paragraph (1) of the form of ADR attached as Exhibit A to the Deposit Agreement and in each of the ADRs issued and outstanding under the terms of the Deposit Agreement is hereby amended as of the Effective Date by deleting such sentence in its entirety and inserting the following in its stead:

> "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, and as amended by Amendment No. 1 to the Deposit Agreement, dated as of March 10, 2023 (as so amended and as further 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."

(d) The fourth sentence of paragraph (15) (c) of the form of ADR attached as Exhibit A to the Deposit Agreement and in each of the ADRs issued and outstanding under the terms of the Deposit Agreement is hereby amended as of the Effective Date by deleting such sentence in its entirety and inserting the following in its stead:

"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 (17) 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."

Section 3.2 Change of Ratio. All other references to the ADS-to-Share ratio made in the form of ADR attached as Exhibit A to the Deposit Agreement and in each of the ADRs outstanding, as of the Effective Date, under the terms of the Deposit Agreement shall, as of the Effective Date, refer to the ADS-to-Share ratio of "one (1) ADS to ten (10) Shares."

ARTICLE IV

REPRESENTATIONS AND WARRANTIES

Section 4.1 Representations and Warranties. The Company represents and warrants to, and agrees with, the Depositary and the Holders and Beneficial Owners, that:

(a) This Amendment No. 1, when executed and delivered by the Company, and the Deposit Agreement and all other documentation executed and delivered by the Company in connection therewith, will be and have been, respectively, duly and validly authorized, executed, and delivered by the Company, and constitute the legal, valid, and binding obligations of the Company, enforceable against the Company in accordance with their respective terms, subject to bankruptcy, insolvency, fraudulent transfer, moratorium, and similar laws of general applicability relating to or affecting creditors' rights and to general equity principles; and

(b) In order to ensure the legality, validity, enforceability, or admissibility into evidence of this Amendment No. 1 or the Deposit Agreement as amended hereby, or any other document furnished hereunder or thereunder, none of such agreements need to be filed or recorded with any court or other authority under the laws of England and Wales, nor does any stamp or

similar tax need be paid under the laws of England and Wales on or in respect of such agreements; and

(c) All of the information provided to the Depositary by the Company in connection with this Amendment No. 1 is true, accurate, and correct.

ARTICLE V

MISCELLANEOUS

Section 5.1 New ADRs. From and after the Effective Date, the Depositary shall arrange to have new ADRs printed to reflect the changes to the form of ADR effected by this Amendment No. 1. All ADRs issued hereunder after the Effective Date, whether upon the deposit of Shares or other Deposited Securities or upon the transfer, combination, or split up of existing ADRs, shall be substantially in the form of the specimen ADR attached as Exhibit A hereto. ADRs issued prior or subsequent to the date hereof, which do not reflect the changes to the form of ADR effected hereby, need to be returned to the Depositary for exchange. The Depositary is authorized and directed to take any and all actions deemed necessary to effect the foregoing.

Section 5.2 Notice of Amendment to Holders of ADSs. The Depositary is hereby directed to send a notice informing the Holders of ADSs, *inter alia*, (i) of the terms of this Amendment No. 1, (ii) of the Effective Date of this Amendment No. 1, (iii) that the Holder of ADRs, if any, are requested to surrender their ADRs in exchange for new ADRs reflecting the changes effected by this Amendment No. 1, as provided in Section 5.1 hereof., and (iv) that copies of this Amendment No. 1 may be retrieved from the Commission's website at https://www.sec.gov and may be obtained from the Depositary and the Company upon request. The notice to Holders of ADSs shall be substantially in the form of Exhibit B attached hereto.

Section 5.3 Indemnification. The Company agrees to indemnify and hold harmless the Depositary (and any and all of its directors, employees, and officers) for any and all

liability it or they may incur as a result of the terms of this Amendment No. 1 and the transactions contemplated herein.

Section 5.4 Ratification. Except as expressly amended hereby, the terms, covenants, and conditions of the Deposit Agreement as originally executed shall remain in full force and effect.

Section 5.5 Governing Law. This Amendment No. 1 shall be governed by and construed in accordance with the laws of the State of New York.

Section 5.6 Counterparts. This Amendment No. 1 may be executed in any number of counterparts, each of which shall be deemed an original, and all of such counterparts together shall be deemed an original, and all such counterparts together shall constitute one and the same agreement.

[Signature page on following page]

IN WITNESS WHEREOF, the Company and the Depositary have caused this Amendment No. 1 to be executed by representatives thereunto duly authorized as of the date set forth above.

ORCHARD THERAPEUTICS PLC

By: /s/ Frank Thomas
Name: Frank E. Thomas
Title: President and Chief Operating Officer

CITIBANK, N.A., as Depositary

By: /s/ Leslie DeLuca
Name: Leslie DeLuca
Title: Attorney-in-Fact

EXHIBIT A

FORM OF ADR

Number CUSIP NUMBER: _____

_____

American Depositary Shares (each American Depositary Share representing the right to receive ten (10) fully paid ordinary shares)

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 ten (10) Shares deposited under the Deposit Agreement (as hereinafter defined) with the Custodian, which at the date of the execution of the Deposit Agreement was 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, and as amended by Amendment No.1 to the Deposit Agreement, dated as of March 10, 2023 (as so amended and as further 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.

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(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.

(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 (17) 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

Form of Depositary Notice

NOTICE OF ADS RATIO CHANGE / REVERSE SPLIT

To Holders of American Depositary Shares ("ADSs") of ORCHARD THERAPEUTICS PLC

Company:	ORCHARD THERAPEUTICS PLC**,** a public limited company incorporated under the laws of England and Wales (the "Company").
Depositary:	Citibank, N.A.
Custodian:	Citibank, N.A**.** (London).
Existing ADS-to-Share Ratio:	Each one (1) ADS represents one (1) fully paid ordinary share of the Company (the "Share(s)").
New ADS-to-Share Ratio:	Each one (1) ADS represents ten (10) Shares.
Deposit Agreement:	Deposit Agreement, dated as of November 2, 2018, by and among the Company, the Depositary, and the Holders and Beneficial Owners of ADSs issued thereunder (the "Deposit Agreement").
ADS Symbol:	ORTX.
Existing ADS ISIN:	US68570P1012.
New ADS ISIN:	US68570P2002.
Existing ADS CUSIP:	68570P101.
New ADS CUSIP:	68570P200.
Effective Date:	March 10, 2023.
ADS Books Closure to ADS Issuances and Cancellations:	March 7, 2023 (5:00 p.m. New York City time) until March 10, 2023 (5:00 p.m. New York City time).

The Company and the Depositary have agreed to change the Existing ADS-to-Share Ratio (the "ADS Ratio Change") as of the Effective Date as follows:

Existing ADS-to-Share Ratio: **One (1) ADS to one (1) Share**
New ADS-to-Share Ratio: **One (1) ADS to ten (10) Shares**

Following the Effective Date for the ADS Ratio Change, each ADS will represent ten (10) Shares.

As a result of the ADS Ratio Change, the CUSIP number for the ADSs will change as follows:

Existing ADS CUSIP: 68570P101

New ADS CUSIP: 68570P200

In connection with the ADS Ratio Change, Holders of ADSs as of the Effective Date will be charged a Depositary fee equal to U.S. $0.025 per ADS cancelled.

You do not need to take any action for existing ADSs held via the Direct Registration System (the "DRS"). The new ADSs will be issued as "uncertificated ADSs" in DRS form and will be credited to an account in the name of the existing ADS holders on the books of the Depositary. The DRS statements reflecting the exchange of existing ADSs for new ADSs will be mailed to holders of uncertificated ADSs held via the DRS promptly after the Effective Date.

Holders of ADRs are required to surrender their ADRs to receive their new ADSs at the rate of 0.1 ADS for each existing ADS surrendered.

No fractional ADSs will be issued. Cash in lieu of fractional entitlements to ADSs will be distributed at a rate based upon the net proceeds received by the Depositary for the sale of the aggregate of the fractional ADS entitlements.

The Depositary has filed (x) a form of Amendment No. 1 to the Deposit Agreement, and (y) a form of ADR that reflects the new ADS-to-Share ratio with the U.S. Securities and Exchange Commission (the "SEC") under cover of Post-Effective Amendment No. 1 to Registration Statement on Form F-6. A copy of the filing is available from the SEC's website at www.sec.gov under Registration Number 333-227905.

If you have any questions about the above amendment and exchange, please call Citibank ADR Shareholder Services at 1-877-248-4237. Copies of the Deposit Agreement and of Amendment No. 1 to the Deposit Agreement are available at the principal offices of the Depositary at 388 Greenwich Street, New York, NY 10013 and can also be retrieved from the SEC's website at www.sec.gov under Registration Number 333-227905.

Date: March 10, 2023 Citibank, N.A. as Depositary

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DESCRIPTION OF SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

The following description is a summary of the material terms of Orchard Therapeutics plc (the "Company") American Depositary Shares ("ADSs"), each representing ten ordinary shares, nominal value £0.10 per share. This description also summarizes relevant provisions of English law. The following summary does not purport to be complete and is subject to, and is qualified in its entirety by reference to, the applicable provisions of English law and the Company's articles of association (the "Articles"), a copy of which is incorporated by reference as Exhibit 3.1 to the Annual Report on Form 10-K, of which this Exhibit 4.5 is a part. We encourage you to read the Articles and the applicable provisions of English law for additional information.

DESCRIPTION OF SHARE CAPITAL

Certain resolutions were passed by the Company's shareholders at its 2021 annual general shareholder meeting. These include resolutions for the:

- general authorization of the Company's directors for purposes of Section 551 of the U.K. Companies Act 2006 to issue shares in the Company and grant rights to subscribe for or convert any securities into shares in the Company up to a maximum aggregate nominal amount of £13,023,851.50 for a period of five years from the date of the meeting; and

- empowering of the Company's directors pursuant to Section 570 of the U.K. Companies Act 2006 to issue equity securities for cash pursuant to the Section 551 authority referred to above as if the statutory preemption rights under Section 561(1) of the U.K. Companies Act 2006 did not apply to such allotments.

Issued share capital

As of December 31, 2022, the Company's issued share capital was 126,947,225 ordinary shares with a nominal value of £0.10 per share. No non-voting ordinary shares, nominal value of £0.10 per share, were issued and outstanding as of December 31, 2022.

Ordinary shares

In accordance with the Articles, the following summarizes the rights of holders of the Company's ordinary shares:

- each holder of the Company's ordinary shares is entitled to one vote per ordinary share on all matters to be voted on by shareholders generally;

- the holders of the Company's ordinary shares are entitled to receive notice of, attend, speak and vote at the Company's general meetings; and

- the holders of the Company's ordinary shares are entitled to receive such dividends as are recommended by the Company's directors and declared by the Company's shareholders.

Non-Voting Ordinary Shares

In accordance with their terms of issue, the Company's non-voting ordinary shares have the same rights and restrictions as ordinary shares and shall otherwise rank pari passu in all respects, except that:

- each holder of the Company's non-voting ordinary shares is not entitled to receive notice of, or attend or vote at, any general meeting of shareholders (save in relation to variation of class rights attaching to the non-voting ordinary shares);
- the non-voting ordinary shares shall be non-transferable; and

- Subject to the terms of issue, the non-voting ordinary shares may be redesignated as ordinary shares by the board of directors of the Company, or a duly authorised representative thereof, only upon receipt of a redesignation notice from the holder of the non-voting ordinary shares.

Registered shares

The Company is required by the U.K. Companies Act 2006 to keep a register of its shareholders. Under English law, the shares are deemed to be issued when the name of the shareholder is entered in the Company's share register. The share register therefore is prima facie evidence of the identity of the Company's shareholders, and the shares that they hold. The share register generally provides limited, or no, information regarding the ultimate beneficial owners of the Company's shares. The Company's share register is maintained by the Company's registrar. Holders of the Company's ADSs are not treated as one of its shareholders and their names are therefore not entered in the Company's share register. The depositary, the custodian or their nominees is the holder of the shares underlying the Company's ADSs. Holders of the Company's ADSs have a right to receive the ordinary shares underlying their ADSs. For a discussion of the Company's ADSs and ADS holder rights, see "Description of American Depositary Shares" below.

Under the U.K. Companies Act 2006, the Company must enter an allotment of shares in its share register as soon as practicable and in any event within two months of the allotment. The Company is also required by the U.K. Companies Act 2006 to register a transfer of shares (or give the transferee notice of and reasons for refusal as the transferee may reasonably request) as soon as practicable and in any event within two months of receiving notice of the transfer.

The Company, any of its shareholders or any other affected person may apply to the court for rectification of the share register if:

- the name of any person, without sufficient cause, is wrongly entered in or omitted from the Company's register of members; or

- there is a default or unnecessary delay in entering on the register the fact of any person having ceased to be a member or on which the Company has a lien, provided that such delay does not prevent dealings in the shares taking place on an open and proper basis.

Preemptive rights

English law generally provides shareholders with preemptive rights when new shares are issued for cash; however, it is possible for the articles of association, or shareholders in general meeting, to exclude preemptive rights. Such an exclusion of preemptive rights may be for a maximum period of up to five years from the date of adoption of the articles of association, if the exclusion is contained in the articles of association, or from the date of the shareholder resolution, if the exclusion is by shareholder resolution. In either case, this exclusion would need to be renewed by the Company's shareholders upon its expiration (i.e., at least every five years). At the Company's annual general meeting in June 2021, the Company's shareholders approved the exclusion of preemptive rights for a period of five years from the date of approval, which exclusion will need to be renewed upon expiration (i.e., at least every five years) to remain effective, but may be sought more frequently for additional five-year terms (or any shorter period).

Registration rights

Certain holders of the Company's ordinary shares are entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of an investment and shareholders' agreement between the Company and holders of its convertible preferred shares, which were subsequently converted into ordinary shares in connection with the Company's initial public offering in November 2018. The investment and shareholders' agreement includes demand registration rights, short-form registration rights and piggyback registration rights.

Demand registration rights

Certain holders of the Company's ordinary shares are entitled to demand registration rights. Under the terms of the investment and shareholders' agreement, the Company will be required, upon the written request of holders of a

majority of these securities to file a registration statement and use best efforts to effect the registration of all or a portion of these shares for public resale.

Short-form registration rights
Pursuant to the investment and shareholders' agreement, if the Company is eligible to file a registration statement on Form F-3 or Form S-3, upon the written request of holders of a majority of these securities at an aggregate offer price of at least $5.0 million, the Company will be required to effect a registration of such shares. The Company is required to effect only two registrations in any twelve month period pursuant to this provision of the investment and shareholders' agreement. The right to have such shares registered on Form F-3 or Form S-3 is further subject to other specified conditions and limitations.

Piggyback registration rights
Pursuant to the investment and shareholders' agreement, if the Company registers any of its securities either for its own account or for the account of other security holders, other than in connection with the Company's initial public offering or a registration for any employee benefit plan, corporate reorganization, or the offer or sale of debt securities, the holders of these shares are entitled to include their shares in the registration. Subject to certain exceptions contained in the investment and shareholders' agreement, the Company and the underwriters may limit the number of shares included in the underwritten offering to the number of shares which the Company and the underwriters determine in their sole discretion will not jeopardize the success of the offering.

Indemnification
The investors' rights agreement contains customary cross-indemnification provisions, under which the Company is obligated to indemnify holders of registrable securities in the event of material misstatements or omissions in the registration statement attributable to the Company, and they are obligated to indemnify the Company for material misstatements or omissions attributable to them.

Expiration of registration rights
The registration rights granted under the investment and shareholders' agreement will terminate with respect to such holder on the earliest of (i) a deemed liquidation event, as defined in the Company's Articles of Association, (ii) the fifth anniversary of the completion of the Company's initial public offering in November 2018 and (iii) such time as SEC Rule 144 under the Securities Act of 1933, as amended (the "Securities Act") or another similar exemption under the Securities Act is available for the sale of all of such holder's shares without limitation during a three-month period without registration.

Articles of association

The Company's current Articles were adopted by its shareholders at its 2020 annual general shareholder meeting and have been publicly filed with the Securities and Exchange Commission. A summary of the terms of the Articles, and the relevant provisions of applicable English law, is set out below. The summary below does not purport to be complete and is qualified in its entirety by reference to applicable English law.

The Articles contain no specific restrictions on the Company's purpose and therefore, by virtue of section 31(1) of the U.K. Companies Act 2006, the Company's purpose is unrestricted.

Share capital

As of the date of this Annual Report on Form 10-K, of which this Exhibit 4.5 is a part, the Company's share capital consists of ordinary shares and non-voting ordinary shares. The Company may issue shares with such rights or restrictions as may be determined by ordinary resolution, including shares which are to be redeemed, or are liable to be redeemed at the Company's option or the holder of such shares.

Voting

The holders of ordinary shares have the right to receive notice of, and to vote at, the Company's general meetings. Each shareholder who is present in person (or, being a corporation, by representative) at a general meeting on a show of hands has one vote and, on a poll, every such holder who is present in person (or, being a corporation, by

representative) or by proxy has one vote in respect of every share held by him. The holders of non-voting ordinary shares do not have the right to receive notice of, and to vote at, the Company's general meetings.

Variation of rights

Whenever the Company's share capital is divided into different classes of shares, the special rights attached to any class may be varied or abrogated either with the consent in writing of the holders of not less than three-quarters in nominal value of the issued shares of that class or with the sanction of a special resolution passed at a general meeting of the holders of the shares of that class and may be so varied and abrogated whilst the company is a going concern.

Dividends

The Company may, subject to the provisions of the U.K. Companies Act 2006 and the Articles, by ordinary resolution from time to time declare dividends to be paid to shareholders not exceeding the amount recommended by the Company's board of directors. Subject to the provisions of the U.K. Companies Act 2006, in so far as, in the board of directors' opinions, the Company's profits justify such payments, the board of directors may pay interim dividends on any class of the Company's shares.

Any dividend unclaimed after a period of 12 years from the date such dividend was declared or became payable shall, if the board of directors resolve, be forfeited and shall revert to the Company. No dividend or other moneis payable on or in respect of a share shall bear interest as against the Company.

Liquidation Preference

On a distribution of assets on a liquidation, the surplus assets remaining after payment of liabilities shall be distributed among the holders of ordinary shares pro rata to the number of ordinary shares held.

Transfer of ordinary shares

Each member may transfer all or any of his shares which are in certificated form by means of an instrument of transfer in any usual form or in any other form which the board of directors may approve. Each member may transfer all or any of his shares which are in uncertificated form by means of a "relevant system" (i.e., the CREST System) in such manner provided for, and subject as provided in, the CREST Regulations.

The Company's board of directors may, in its absolute discretion, refuse to register a transfer of certificated shares unless:

(i) it is for a share which is fully paid up;

(ii) it is for a share upon which the Company has no lien;

(iii) it is only for one class of share;

(iv) it is in favor of a single transferee or no more than four joint transferees;

(v) it is duly stamped or is duly certificated or otherwise shown to the satisfaction of the board of directors to be exempt from stamp duty; and

(vi) it is delivered for registration to the registered office of the Company (or such other place as the board of directors may determine), accompanied (except in the case of a transfer by a person to whom the company is not required by law to issue a certificate and to whom a certificate has not been issued or in the case of a renunciation) by the certificate for the shares to which it relates and such other evidence as the board of directors may reasonably require to prove the title of the transferor (or person renouncing) and the due execution of the transfer or renunciation by him or, if the transfer or renunciation is executed by some other person on his behalf, the authority of that person to do so.

The board of directors may refuse to register a transfer of uncertificated shares in any circumstances that are allowed or required by the CREST Regulations and the CREST System.

Allotment of shares and preemption rights

Subject to the U.K. Companies Act 2006 and to any rights attached to existing shares, any share may be issued with or have attached to it such rights and restrictions as the Company may by ordinary resolution determine, or if no ordinary resolution has been passed or so far as the resolution does not make specific provision, as the board of directors may determine (including shares which are to be redeemed, or are liable to be redeemed at the option of the Company or the holder of such shares).

In accordance with section 551 of the U.K. Companies Act 2006, the board of directors may be generally and unconditionally authorized to exercise all the powers of the Company to allot shares up to an aggregate nominal amount equal to the amount stated in the relevant ordinary resolution authorizing such allotment. The authorities referred to above were included in the special resolution passed in June 2021 and remain in force at the date of this Annual Report on Form 10-K, of which this Exhibit 4.5 is a part.

The provisions of section 561 of the U.K. Companies Act 2006 (which confer on shareholders rights of preemption in respect of the allotment of equity securities which are paid up in cash) apply to the Company except to the extent disapplied by special resolution of the Company. Such preemption rights have been disapplied pursuant to the special resolution passed at the Company's annual general meeting in June 2021.

Alteration of share capital

The Company may by ordinary resolution consolidate or divide all of its share capital into shares of larger nominal value than its existing shares, or cancel any shares which, at the date of the ordinary resolution, have not been taken or agreed to be taken by any person and diminish the amount of its share capital by the nominal amount of shares so cancelled or sub-divide its shares, or any of them, into shares of smaller nominal value.

The Company may, in accordance with the U.K. Companies Act 2006, reduce or cancel its share capital or any capital redemption reserve or share premium account in any manner and with and subject to any conditions, authorities and consents required by law.

Board of directors

Unless otherwise determined by the Company by ordinary resolution, the number of directors (other than any alternate directors) shall not be less than two, but there shall be no maximum number of directors.

Subject to the Articles and the U.K. Companies Act 2006, the Company may by ordinary resolution appoint a person who is willing to act as a director and the board of directors shall have power at any time to appoint any person who is willing to act as a director, in both cases either to fill a vacancy or as an addition to the existing board of directors.

The Articles provide that the Company's board of directors will be divided into three classes, each of which will consist, as nearly as possible, of one-third of the total number of directors constituting the Company's entire board and which will serve staggered three-year terms. At each annual general meeting, the successors of directors whose terms then expire will be elected to serve from the time of election and qualification until the third annual meeting following election.

At every subsequent annual general meeting any director who either (i) has been appointed by the board of directors since the last annual general meeting or (ii) was not appointed or reappointed at one of the preceding two annual general meetings, must retire from office and may offer themselves for reappointment by the shareholders by ordinary resolution.

Subject to the provisions of the Articles, the board of directors may regulate their proceedings as they deem appropriate. A director may, and the secretary at the request of a director shall, call a meeting of the directors.

The quorum for a meeting of the board of directors shall be fixed from time to time by a decision of the board of directors, but it must never be less than two and unless otherwise fixed, it is two.

Questions and matters requiring resolution arising at a meeting shall be decided by a majority of votes of the participating directors, with each director having one vote. In the case of an equality of votes, the chairperson will have a second or casting vote (unless the chairperson is not entitled to vote on the resolution in question).

Directors shall be entitled to receive such remuneration as the board of directors shall determine for their services to the Company as directors, and for any other service which they undertake for the Company provided that the aggregate fees payable to the directors must not exceed £250,000 per annum. The directors shall also be entitled to be paid all reasonable expenses properly incurred by them in connection with their attendance at meetings of shareholders or class meetings, board of director or committee meetings or otherwise in connection with the exercise of their powers and the discharge of their responsibilities in relation to the Company.

The board of directors may, in accordance with the requirements in the Articles, authorize any matter proposed to them by any director which would, if not authorized, involve a director breaching his duty under the U.K. Companies Act 2006, to avoid conflicts of interests.

A director seeking authorization in respect of such conflict shall declare to the board of directors the nature and extent of his interest in a conflict as soon as is reasonably practicable. The director shall provide the board with such details of the matter as are necessary for the board to decide how to address the conflict together with such additional information as may be requested by the board of directors.

Any authorization by the board of directors will be effective only if:

(i) to the extent permitted by the U.K. Companies Act 2006, the matter in question shall have been proposed by any director for consideration in the same way that any other matter may be proposed to the directors under the provisions of the Articles;

(ii) any requirement as to the quorum for consideration of the relevant matter is met without counting the conflicted director and any other conflicted director; and

(iii) the matter is agreed to without the conflicted director voting or would be agreed to if the conflicted director's and any other interested director's vote is not counted.

Subject to the provisions of the U.K. Companies Act 2006, every director, secretary or other officer of the Company (other than an auditor) is entitled to be indemnified against all costs, charges, losses, damages and liabilities incurred by him in the actual purported exercise or discharge of his duties or exercise of his powers or otherwise in relation to them.

General meetings

The Company must convene and hold general meetings in accordance with the U.K. Companies Act 2006. Under the U.K. Companies Act 2006, an annual general meeting must be called by notice of at least 21 clear days and a general meeting must be called by notice of at least 14 clear days.

No business shall be transacted at any general meeting unless a quorum is present when the meeting proceeds to business, but the absence of a quorum shall not preclude the choice or appointment of a chairperson of the meeting, which shall not be treated as part of the business of the meeting. Save as otherwise provided by the Articles, shareholders holding thirty-three and one-third percent (33 1/3%) of the Company's issued shares (excluding any shares held as treasury shares) present in person or by proxy (or in the case of a corporation, by a representative) and entitled to vote shall be a quorum for all purposes.

Borrowing Powers

Subject to the Articles and the U.K. Companies Act 2006, the board of directors may exercise all of the powers of the company to:

(a) borrow money;

(b) indemnify and guarantee;

(c) mortgage or charge;

(d) create and issue debentures and other securities; and

(e) give security either outright or as collateral security for any debt, liability or obligation of the company or of any third party.

Capitalization of profits

The directors may, if they are so authorized by an ordinary resolution of the shareholders, decide to capitalize any undivided profits of the company (whether or not they are available for distribution), or any sum standing to the credit of the Company's share premium account or capital redemption reserve. The directors may also, subject to the aforementioned ordinary resolution, appropriate any sum which they so decide to capitalize to the persons who would have been entitled to it if it were distributed by way of dividend and in the same proportions.

Uncertificated shares

Subject to the U.K. Companies Act 2006, the board of directors may permit title to shares of any class to be issued or held otherwise than by a certificate and to be transferred by means of a "relevant system" (i.e., the CREST System) without a certificate.

The board of directors may take such steps as it sees fit in relation to the evidencing of and transfer of title to uncertificated shares, any records relating to the holding of uncertificated shares and the conversion of uncertificated shares to certificated shares, or vice-versa.

The Company may by notice to the holder of an uncertificated share, require that share to be converted into certificated form.

The board of directors may take such other action that the board considers appropriate to achieve the sale, transfer, disposal, forfeiture, re-allotment or surrender of an uncertified share or otherwise to enforce a lien in respect of it.

Stock exchange listing

The Company's ADSs have been listed on the Nasdaq Global Select Market under the symbol "ORTX" since October 31, 2018.

Transfer agent and registrar of shares

The Company's share register is maintained by Equiniti Limited. The share register is prima facie evidence of the identity of the Company's shareholders, and the shares that they hold. Holders of the Company's ADSs are not treated as the Company's shareholders and their names are therefore not entered in the Company's share register. The depositary, the custodian or their nominees is the holder of the ordinary shares underlying the Company's ADSs. Holders of the Company's ADSs have a right to receive the ordinary shares underlying their ADSs. For a discussion of the Company's ADSs and ADS holder rights, see "Description of American Depositary Shares" below.

DESCRIPTION OF AMERICAN DEPOSITARY SHARES

Citibank, N.A., or Citibank, is the depositary for the ADSs. Citibank's depositary offices are located at, 388 Greenwich Street, New York, New York 10013. ADSs represent ownership interests in securities that are on deposit with the depositary. ADSs may be represented by certificates that are commonly known as American Depositary

Receipts (“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.

The Company has appointed Citibank as depositary pursuant to a deposit agreement. A copy of the deposit agreement is on file with the Securities and Exchange Commission (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 website (www.sec.gov). Please refer to registration number 333-227905 when retrieving such copy.

The following is a summary description of the material terms of the ADSs and of the material rights of owners of ADSs. Summaries by their nature lack the precision of the information summarized and that the rights and obligations of an owner of ADSs will be determined by reference to the terms of the deposit agreement and not by this summary. We urge you to review the deposit agreement in its entirety.

Each ADS represents the right to receive, and to exercise the beneficial ownership interests in, ten ordinary shares that is on deposit with the depositary and/or custodian. An ADS also represents the right to receive, and to exercise the beneficial interests in, any other property received by the depositary or the custodian on behalf of the owner of the ADS but that has not been distributed to the owners of ADSs because of legal restrictions or practical considerations. The Company and the depositary may agree to change the ADS-to-ordinary share ratio by amending the deposit agreement. This amendment may give rise to, or change, the depositary fees payable by ADS owners. The custodian, the depositary and their respective nominees will hold all deposited property for the benefit of the holders and beneficial owners of ADSs. The deposited property does not constitute the proprietary assets of the depositary, the custodian or their nominees. Beneficial ownership in the deposited property will under the terms of the deposit agreement be vested in the beneficial owners of the ADSs. The depositary, the custodian and their respective nominees will be the record holders of the deposited property represented by the ADSs for the benefit of the holders and beneficial owners of the corresponding ADSs. A beneficial owner of ADSs may or may not be the holder of ADSs. Beneficial owners of ADSs will be able to receive, and to exercise beneficial ownership interests in, the deposited property only through the registered holders of the ADSs, the registered holders of the ADSs (on behalf of the applicable ADS owners) only through the depositary, and the depositary (on behalf of the owners of the corresponding ADSs) directly, or indirectly, through the custodian or their respective nominees, in each case upon the terms of the deposit agreement.

Owners of the Company’s ADSs will become a party to the deposit agreement and therefore will be bound to its terms and to the terms of any ADR that represents such ADSs. The deposit agreement and the ADR specify the Company’s rights and obligations as well as the rights and obligations of owners of ADSs and those of the depositary. ADS holders appoint the depositary to act on their behalf in certain circumstances. The deposit agreement and the ADRs are governed by New York law. However, the Company’s obligations to the holders of ordinary shares will continue to be governed by the laws of England and Wales, which may be different from the laws of the United States.

In addition, applicable laws and regulations may require holders of ADSs to satisfy reporting requirements and obtain regulatory approvals in certain circumstances. Holders of ADSs are solely responsible for complying with such reporting requirements and obtaining such approvals. Neither the depositary, the custodian, the Company or any of their or the Company’s respective agents or affiliates shall be required to take any actions whatsoever on behalf of holders of ADSs to satisfy such reporting requirements or obtain such regulatory approvals under applicable laws and regulations.

Owners of ADSs will not be treated as one of the Company’s shareholders and will not have direct shareholder rights. The depositary will hold on the ADS holders’ behalf the shareholder rights attached to the ordinary shares underlying such ADSs. Owners of ADSs will be able to exercise the shareholders rights for the ordinary shares represented by such ADSs through the depositary only to the extent contemplated in the deposit agreement. To exercise any shareholder rights not contemplated in the deposit agreement a holder of ADSs will, as an ADS owner, need to arrange for the cancellation of such ADSs and become a direct shareholder.

The manner in which ADSs are owned (e.g., in a brokerage account vs. as registered holder, or as holder of certificated vs. uncertificated ADSs) may affect the rights and obligations, and the manner in which, and extent to

which, the depositary's services are made available to the holder of ADSs. Owners of ADSs may hold their ADSs either by means of an ADR registered in their name, through a brokerage or safekeeping account, or through an account established by the depositary in their name reflecting the registration of uncertificated ADSs directly on the books of the depositary (commonly referred to as the direct registration system or DRS). The direct registration system reflects the uncertificated (book-entry) registration of ownership of ADSs by the depositary. Under the direct registration system, ownership of ADSs is evidenced by periodic statements issued by the depositary to the holders of the ADSs. The direct registration system includes automated transfers between the depositary and The Depository Trust Company, or DTC, the central book-entry clearing and settlement system for equity securities in the United States. If an ADS owner decides to hold their ADSs through their brokerage or safekeeping account, such holder must rely on the procedures of their broker or bank to assert their rights as ADS owner. Banks and brokers typically hold securities such as the ADSs through clearing and settlement systems such as DTC. The procedures of such clearing and settlement systems may limit such holder's ability to exercise their rights as an owner of ADSs. ADS owners should consult with their broker or bank if they have any questions concerning these limitations and procedures. All ADSs held through DTC will be registered in the name of a nominee of DTC. This summary description assumes holders of ADSs have opted to own the ADSs directly by means of an ADS registered in their name and, as such, refers to the owner as the "holder." This summary also assumes holders will own ADSs at the relevant time.

The registration of the ordinary shares in the name of the depositary or the custodian shall, to the maximum extent permitted by applicable law, vest in the depositary or the custodian the record ownership in the applicable ordinary shares with the beneficial ownership rights and interests in such ordinary shares being at all times vested with the beneficial owners of the ADSs representing the ordinary shares. The depositary or the custodian shall at all times be entitled to exercise the beneficial ownership rights in all deposited property, in each case only on behalf of the holders and beneficial owners of the ADSs representing the deposited property.

Dividends and other distributions

Holders of ADSs generally have the right to receive the distributions the Company makes on the securities deposited with the custodian. Receipt of these distributions by an ADS holder may be limited, however, by practical considerations and legal limitations. Holders of ADSs will receive such distributions under the terms of the deposit agreement in proportion to the number of ADSs held as of the specified record date, after deduction the applicable fees, taxes and expenses.

Distributions of cash

Whenever the Company makes a cash distribution for the securities on deposit with the custodian, the Company will deposit the funds with the custodian. Upon receipt of confirmation of the deposit of the requisite funds, the depositary will arrange for the funds received in a currency other than U.S. Dollars to be converted into U.S. Dollars and for the distribution of the U.S. Dollars to the holders, subject to the laws and regulations of England and Wales.

The conversion into U.S. Dollars will take place only if practicable and if the U.S. Dollars are transferable to the United States. The depositary will apply the same method for distributing the proceeds of the sale of any property (such as undistributed rights) held by the custodian in respect of securities on deposit.

The distribution of cash will be made net of the fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. The depositary will hold any cash amounts it is unable to distribute in a non-interest bearing account for the benefit of the applicable holders and beneficial owners of ADSs until the distribution can be effected or the funds that the depositary holds must be escheated as unclaimed property in accordance with the laws of the relevant states of the United States.

Distributions of shares

Whenever the Company makes a free distribution of ordinary shares for the securities on deposit with the custodian, the Company will deposit the applicable number of ordinary shares with the custodian. Upon receipt of confirmation of such deposit, the depositary will either distribute to holders new ADSs representing the ordinary shares deposited

or modify the ADS-to-ordinary shares ratio, in which case each ADS held will represent rights and interests in the additional ordinary shares so deposited. Only whole new ADSs will be distributed. Fractional entitlements will be sold and the proceeds of such sale will be distributed as in the case of a cash distribution.

The distribution of new ADSs or the modification of the ADS-to-ordinary share ratio upon a distribution of ordinary shares will be made net of the fees, expenses, taxes, and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes or governmental charges, the depositary may sell all or a portion of the new ordinary shares so distributed.

No such distribution of new ADSs will be made if it would violate a law (e.g., the U.S. securities laws) or if it is not operationally practicable. If the depositary does not distribute new ADSs as described above, it may sell the ordinary shares received upon the terms described in the deposit agreement and will distribute the proceeds of the sale as in the case of a distribution of cash.

Distributions of rights

Whenever the Company intends to distribute rights to purchase additional ordinary shares, the Company will give prior notice to the depositary and will assist the depositary in determining whether it is lawful and reasonably practicable to distribute rights to purchase additional ADSs to holders.

The depositary will establish procedures to distribute rights to purchase additional ADSs to holders and to enable such holders to exercise such rights if it is lawful and reasonably practicable to make the rights available to holders of ADSs, and if the Company provides all of the documentation contemplated in the deposit agreement (such as opinions to address the lawfulness of the transaction). Holders of ADSs may have to pay fees, expenses, taxes and other governmental charges to subscribe for the new ADSs upon the exercise of their rights. The depositary is not obligated to establish procedures to facilitate the distribution and exercise by holders of rights to purchase new ordinary shares other than in the form of ADSs.

The depositary will *not* distribute the rights to an ADS holder if:

- the Company does not timely request that the rights be distributed to such holders or the Company requests that the rights not be distributed to such holders;
- the Company fails to deliver satisfactory documents to the depositary; or
- it is not reasonably practicable to distribute the rights.

The depositary will sell the rights that are not exercised or not distributed if such sale is lawful and reasonably practicable. The proceeds of such sale will be distributed to holders as in the case of a cash distribution. If the depositary is unable to sell the rights, it will allow the rights to lapse.

Elective Distributions

Whenever the Company intends to distribute a dividend payable at the election of shareholders either in cash or in additional shares, the Company will give prior notice thereof to the depositary and will indicate whether the Company wishes the elective distribution to be made available to ADS holders. In such case, the Company will assist the depositary in determining whether such distribution is lawful and reasonably practicable.

The depositary will make the election available to ADS holders only if it is reasonably practicable and if the Company has provided all of the documentation contemplated in the deposit agreement. In such case, the depositary will establish procedures to enable ADS holders to elect to receive either cash or additional ADSs, in each case as described in the deposit agreement.

If the election is not made available to ADS holders, ADS holders will receive either cash or additional ADSs, depending on what a shareholder in England and Wales would receive upon failing to make an election, as more fully described in the deposit agreement.

Other Distributions

Whenever the Company intends to distribute property other than cash, ordinary shares or rights to purchase additional ordinary shares, the Company will notify the depositary in advance and will indicate whether the Company wishes such distribution to be made to ADS holders. If so, the Company will assist the depositary in determining whether such distribution to holders is lawful and reasonably practicable.

If it is reasonably practicable to distribute such property to ADS holders and if the Company provides all of the documentation contemplated in the deposit agreement, the depositary will distribute the property to the holders in a manner it deems practicable.

The distribution will be made net of fees, expenses, taxes and governmental charges payable by holders under the terms of the deposit agreement. In order to pay such taxes and governmental charges, the depositary may sell all or a portion of the property received.

The depositary will *not* distribute the property to holders of ADSs and will sell the property if:

- the Company does not request that the property be distributed to holders of ADSs or if the Company asks that the property not be distributed to holders of ADSs; or
- the Company does not deliver satisfactory documents to the depositary; or
- the depositary determines that all or a portion of the distribution to holders of ADSs is not reasonably practicable.

The proceeds of such a sale will be distributed to holders as in the case of a cash distribution.

Redemption

Whenever the Company decides to redeem any of the ordinary shares on deposit with the custodian, the Company will notify the depositary in advance. If it is practicable and if the Company provides all of the documentation contemplated in the deposit agreement, the depositary will provide notice of the redemption to the holders.

The custodian will be instructed to surrender the ordinary shares being redeemed against payment of the applicable redemption price. The depositary will convert the redemption funds received into U.S. Dollars upon the terms of the deposit agreement and will establish procedures to enable holders to receive the net proceeds from the redemption upon surrender of their ADSs to the depositary. ADS holders may have to pay fees, expenses, taxes and other governmental charges upon the redemption of their ADSs. If less than all ADSs are being redeemed, the ADSs to be retired will be selected by lot or on a pro rata basis, as the depositary may determine.

Changes affecting ordinary shares

The ordinary shares held on deposit for ADSs may change from time to time. For example, there may be a change in nominal or par value, split-up, cancellation, consolidation, or any other reclassification of such ordinary shares or a recapitalization, reorganization, merger, consolidation, or sale of assets of the Company.

If any such change were to occur, the ADSs would, to the extent permitted by law, represent the right to receive the property received or exchanged in respect of the ordinary shares held on deposit. The depositary may in such circumstances deliver new ADSs to the holders, amend the deposit agreement, the ADRs and the applicable Registration Statement(s) on Form F-6, call for the exchange of existing ADSs for new ADSs and take any other

actions that are appropriate to reflect as to the ADSs the change affecting the ordinary shares. If the depositary may not lawfully distribute such property to the holders of ADSs, the depositary may sell such property and distribute the net proceeds to such holders as in the case of a cash distribution.

Issuance of ADSs upon deposit of ordinary shares

The depositary may create ADSs on behalf of a holder if such holder or their broker deposits ordinary shares with the custodian. The depositary will deliver these ADSs to the person such holder indicates only after such holder pays any applicable issuance fees and any charges and taxes payable for the transfer of the ordinary shares to the custodian. The ability for a holder to deposit ordinary shares and receive ADSs may be limited by the legal considerations in the United States and England and Wales applicable at the time of deposit.

The issuance of ADSs may be delayed until the depositary or the custodian receives confirmation that all required approvals have been given and that the ordinary shares have been duly transferred to the custodian. The depositary will only issue ADSs in whole numbers.

When a holder makes a deposit of ordinary shares, such holder will be responsible for transferring good and valid title to the depositary. As such, the holder will be deemed to represent and warrant that:

- the ordinary shares are duly authorized, validly issued, fully paid, non-assessable, and legally obtained;
- all preemptive (and similar) rights, if any, with respect to such ordinary shares have been validly waived or exercised;
- the holder is duly authorized to deposit the ordinary shares;
- the ordinary shares presented for deposit are free and clear of any lien, encumbrance, security interest, charge, mortgage, or adverse claim, and are not, and the ADSs issuable upon such deposit will not be, “restricted securities” (as defined in the deposit agreement);
- the ordinary shares presented for deposit have not been stripped of any rights or entitlements; and
- the deposit of shares does not violate any applicable provision of English law.

If any of the representations or warranties are incorrect in any way, the Company and the depositary may, at the holder’s cost and expense, take any and all actions necessary to correct the consequences of the misrepresentations.

Transfer, combination and split up of ADRs

ADR holders will be entitled to transfer, combine or split up their ADRs and the ADSs evidenced thereby. For transfers of ADRs, a holder will have to surrender the ADRs to be transferred to the depositary and also must:

- ensure that the surrendered ADR is properly endorsed or otherwise in proper form for transfer;
- provide such proof of identity and genuineness of signatures as the depositary deems appropriate;
- provide any transfer stamps required by the State of New York or the United States; and
- pay all applicable fees, charges, expenses, taxes, and other government charges payable by ADR holders pursuant to the terms of the deposit agreement, upon the transfer of ADRs.

To have ADRs either combined or split up, a holder must surrender the ADRs in question to the depositary with their request to have them combined or split up, and such holder must pay all applicable fees, charges and expenses payable by ADR holders, pursuant to the terms of the deposit agreement, upon a combination or split up of ADRs.

Withdrawal of ordinary shares upon cancellation of ADSs

Holders are entitled to present their ADSs to the depositary for cancellation and then receive the corresponding number of underlying ordinary shares at the custodian's offices. The ability of a holder to withdraw the ordinary shares held in respect of the ADSs may be limited by the legal consideration in the United States and England and Wales applicable at the time of withdrawal. In order to withdraw the ordinary shares represented by ADSs, a holder will be required to pay to the depositary the fees for cancellation of ADSs and any charges and taxes payable upon the transfer of the ordinary shares. Holders assume the risk for delivery of all funds and securities upon withdrawal. Once canceled, the ADSs will not have any rights under the deposit agreement.

The depositary may ask holders who hold ADSs registered in their name to provide proof of identity and genuineness of any signature and such other documents as the depositary may deem appropriate before it will cancel such holders' ADSs. The withdrawal of the ordinary shares represented by ADSs may be delayed until the depositary receives satisfactory evidence of compliance with all applicable laws and regulations. The depositary will only accept ADSs for cancellation that represent a whole number of securities on deposit.

ADS holders have the right to withdraw the securities represented by their ADSs at any time except as a result of:

- temporary delays that may arise because (i) the transfer books for the ordinary shares or ADSs are closed, or (ii) ordinary shares are immobilized on account of a shareholders' meeting or a payment of dividends;
- obligations to pay fees, taxes and similar charges;
- restrictions imposed because of laws or regulations applicable to ADSs or the withdrawal of securities on deposit; and
- other circumstances specifically contemplated by Section I.A.(I) of the General Instructions to Form F-6 (as such General Instructions may be amended from time to time)

The deposit agreement may not be modified to impair ADS holders' right to withdraw the ordinary shares represented by their ADSs except to comply with mandatory provisions of law.

Voting rights

ADS holders generally have the right under the deposit agreement to instruct the depositary to exercise the voting rights for the ordinary shares represented by their ADSs. The voting rights of holders of ordinary shares are described in "Description of share capital and articles of association-Articles of association" above.

At the Company's request, the depositary will distribute to ADS holders any notice of shareholders' meeting received from the Company together with information explaining how to instruct the depositary to exercise the voting rights of the ordinary shares represented by ADSs. In lieu of distributing such materials, the depositary bank may distribute to holders of ADSs instructions on how to retrieve such materials upon request.

If the depositary timely receives voting instructions from a holder of ADSs, it will endeavor to vote (or cause the custodian to vote) the securities (in person or by proxy) represented by the holder's ADSs as follows:

- *In the event of voting by show of hands*, the depositary will vote (or cause the custodian to vote) all ordinary shares represented by ADSs in accordance with the voting instructions received from a majority of holders of ADSs who provide timely voting instructions.
- *In the event of voting by poll*, the depositary will vote (or cause the custodian to vote) the ordinary shares represented by ADSs in accordance with the voting instructions received from the holders of ADSs.

Securities for which no voting instructions have been received will not be voted (except as otherwise contemplated in the deposit agreement). The ability of the depositary to carry out voting instructions may be limited by practical and legal limitations and the terms of the securities on deposit. The Company cannot assure ADS holders that they will receive voting materials in time to enable them to return voting instructions to the depositary in a timely manner.

Fees and charges

ADS holders are required to pay the following fees under the terms of the deposit agreement:

Service	Fees
• 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

ADS holders are also be responsible to pay certain charges such as:

- taxes (including applicable interest and penalties) and other governmental charges;
- the registration fees as may from time to time be in effect for the registration of ordinary shares on the share register and applicable to transfers of ordinary shares to or from the name of the custodian, the depositary, or any nominees upon the making of deposits and withdrawals, respectively;
- certain cable, telex and facsimile transmission and delivery expenses;
- the expenses and charges incurred by the depositary in the conversion of foreign currency;
- the fees and expenses incurred by the depositary in connection with compliance with exchange control regulations and other regulatory requirements applicable to ordinary shares, ADSs and ADRs; and

- the fees and expenses incurred by the depositary, the custodian or any nominee in connection with the servicing or delivery of deposited property.

ADS fees and charges payable upon (i) the issuance of ADSs, and (ii) the cancellation of ADSs are charged to the person for whom the ADSs are issued (in the case of ADS issuances) and to the person for whom ADSs are cancelled (in the case of ADS cancellations). In the case of ADSs issued by the depositary into DTC, the ADS issuance and cancellation fees and charges may be deducted from distributions made through DTC, and may be charged to the DTC participant(s) receiving the ADSs being issued or the DTC participant(s) holding the ADSs being cancelled, as the case may be, on behalf of the beneficial owner(s) and will be charged by the DTC participant(s) to the account of the applicable beneficial owner(s) in accordance with the procedures and practices of the DTC participants as in effect at the time. ADS fees and charges in respect of distributions and the ADS service fee are charged to the holders as of the applicable ADS record date. In the case of distributions of cash, the amount of the applicable ADS fees and charges is deducted from the funds being distributed. In the case of (i) distributions other than cash and (ii) the ADS service fee, holders as of the ADS record date will be invoiced for the amount of the ADS fees and charges and such ADS fees and charges may be deducted from distributions made to holders of ADSs. For ADSs held through DTC, the ADS fees and charges for distributions other than cash and the ADS service fee may be deducted from distributions made through DTC, and may be charged to the DTC participants in accordance with the procedures and practices prescribed by DTC and the DTC participants in turn charge the amount of such ADS fees and charges to the beneficial owners for whom they hold ADSs.

In the event of refusal to pay the depositary fees, the depositary may, under the terms of the deposit agreement, refuse the requested service until payment is received or may set off the amount of the depositary fees from any distribution to be made to the ADS holder. Certain depositary fees and charges (such as the ADS services fee) may become payable shortly after the closing of the ADS offering. Note that the fees and charges an ADS holder may be required to pay may vary over time and may be changed by the Company and by the depositary. ADS holders will receive prior notice of such changes. The depositary may reimburse the Company for certain expenses incurred by the Company in respect of the ADR program, by making available a portion of the ADS fees charged in respect of the ADR program or otherwise, upon such terms and conditions as the Company and the depositary agree from time to time.

Amendments and termination

The Company may agree with the depositary to modify the deposit agreement at any time without the consent of ADS holders. The Company undertakes to give holders 30 days' prior notice of any modifications that would materially prejudice any of their substantial rights under the deposit agreement. The Company will not consider to be materially prejudicial to ADS holders' substantial rights any modifications or supplements that are reasonably necessary for the ADSs to be registered under the Securities Act or to be eligible for book-entry settlement, in each case without imposing or increasing the fees and charges ADS holders are required to pay. In addition, the Company may not be able to provide ADS holders with prior notice of any modifications or supplements that are required to accommodate compliance with applicable provisions of law.

ADS holders are bound by the modifications to the deposit agreement if such holder continues to hold their ADSs after the modifications to the deposit agreement become effective. The deposit agreement cannot be amended to prevent ADS holders from withdrawing the ordinary shares represented by their ADSs (except as permitted by law).

The Company has the right to direct the depositary to terminate the deposit agreement. Similarly, the depositary may in certain circumstances on its own initiative terminate the deposit agreement. In either case, the depositary must give notice to the holders at least 30 days before termination. Until termination, the rights of ADS holders under the deposit agreement will be unaffected.

Termination

After termination, the depositary will continue to collect distributions received (but will not distribute any such property until an ADS holder requests the cancellation of their ADSs) and may sell the securities held on deposit. After the sale, the depositary will hold the proceeds from such sale and any other funds then held for the holders of ADSs in a non-interest bearing account. At that point, the depositary will have no further obligations to holders

other than to account for the funds then held for the holders of ADSs still outstanding (after deduction of applicable fees, taxes and expenses).

In connection with the termination of the deposit agreement, the depositary may, independently and without the need for any action by the Company, make available to holders a means to withdraw the ordinary shares and other deposited securities represented by their ADSs and to direct the deposit of such ordinary shares and other deposited securities into an unsponsored ADS program established by the depositary, upon such terms and conditions as the depositary may deem reasonably appropriate, subject however, in each case, to satisfaction of the applicable registration requirements by the unsponsored ADS program under the Securities Act, and to receipt by the depositary of payment of the applicable fees and charges of, and reimbursement of the applicable expenses incurred by, the depositary.

Books of depositary

The depositary will maintain ADS holder records at its depositary office. ADS holders may inspect such records at such office during regular business hours but solely for the purpose of communicating with other holders in the interest of business matters relating to the ADSs and the deposit agreement.

The depositary will maintain in New York facilities to record and process the issuance, cancellation, combination, split-up and transfer of ADSs. These facilities may be closed from time to time, to the extent not prohibited by law.

Transmission of notices, reports and proxy soliciting material

The depositary will make available for ADS holders' inspection at its office all communications that it receives from the Company as a holder of deposited securities that the Company makes generally available to holders of deposited securities. Subject to the terms of the deposit agreement, the depositary will send ADS holders copies of those communications or otherwise make those communications available to ADS holders if the Company asks it to.

Limitations on obligations and liabilities

The deposit agreement limits the Company's obligations and the depositary's obligations to holders of the Company's ADSs. Please note the following:

- The Company and the depositary are obligated only to take the actions specifically stated in the deposit agreement without negligence or bad faith.

- The depositary disclaims any liability for any failure to carry out voting instructions, for any manner in which a vote is cast or for the effect of any vote, provided it acts in good faith and in accordance with the terms of the deposit agreement.

- The depositary disclaims any liability for any failure to determine the lawfulness or practicality of any action, for the content of any document forwarded to a holder of ADSs on the Company's behalf or for the accuracy of any translation of such a document, for the investment risks associated with investing in ordinary shares, for the validity or worth of the ordinary shares, for any tax consequences that result from the ownership of ADSs, for the credit-worthiness of any third party, for allowing any rights to lapse under the terms of the deposit agreement, for the timeliness of any of the Company's notices or for the Company's failure to give notice.

- The Company and the depositary are not obligated to perform any act that is inconsistent with the terms of the deposit agreement.

- The Company and the depositary disclaim any liability if the Company or the depositary are prevented or forbidden from or subject to any civil or criminal penalty or restraint on account of, or delayed in, doing or performing any act or thing required by the terms of the deposit agreement, by reason of any provision, present or future of any law or regulation, or by reason of present or future provision of any provision of the Company's Articles of Association or any provision of or governing the securities on deposit, or by reason of any act of God or war or other circumstances beyond the Company's control.

- The Company and the depositary disclaim any liability by reason of any exercise of, or failure to exercise, any discretion provided for in the deposit agreement or in the Company's Articles of Association or in any provisions of or governing the securities on deposit.

- The Company and the depositary further disclaim any liability for any action or inaction in reliance on the advice or information received from legal counsel, accountants, any person presenting ordinary shares for deposit, any holder of ADSs or authorized representatives thereof, or any other person believed by either the Company or the depositary in good faith to be competent to give such advice or information.

- The Company and the depositary also disclaim liability for the inability by a holder to benefit from any distribution, offering, right or other benefit that is made available to holders of ordinary shares but is not, under the terms of the deposit agreement, made available to holders of ADSs.

- The Company and the depositary may rely without any liability upon any written notice, request or other document believed to be genuine and to have been signed or presented by the proper parties.

- The Company and the depositary also disclaim liability for any consequential or punitive damages for any breach of the terms of the deposit agreement.

- No disclaimer of any Securities Act liability is intended by any provision of the deposit agreement.

Nothing in the deposit agreement gives rise to a partnership or joint venture, or establishes a fiduciary relationship, among the Company, the depositary bank and any ADS holder.

Nothing in the deposit agreement precludes Citibank (or its affiliates) from engaging in transactions in which parties adverse to the Company or the ADS owners have interests, and nothing in the deposit agreement obligates Citibank to disclose those transactions, or any information obtained in the course of those transactions, to the Company or to the ADS owners, or to account for any payment received as part of those transactions.

Taxes

ADS holders are responsible for the taxes and other governmental charges payable on the ADSs and the ordinary shares represented by the ADSs. The Company, the depositary and the custodian may deduct from any distribution the taxes and governmental charges payable by holders and may sell any and all property on deposit to pay the taxes and governmental charges payable by holders. ADS holders are liable for any deficiency if the sale proceeds do not cover the taxes that are due.

The depositary may refuse to issue ADSs, to deliver, transfer, split and combine ADRs or to release securities on deposit until all taxes and charges are paid by the applicable holder. The depositary and the custodian may take reasonable administrative actions to obtain tax refunds and reduced tax withholding for any distributions on behalf of the ADS holders. However, holders of ADSs may be required to provide to the depositary and to the custodian proof of taxpayer status and residence and such other information as the depositary and the custodian may require to fulfill legal obligations. Holders of ADSs are required to indemnify the Company, the depositary and the custodian for any claims with respect to taxes based on any tax benefit obtained for such holder.

Foreign currency conversion

The depositary will arrange for the conversion of all foreign currency received into U.S. Dollars if such conversion is practical, and it will distribute the U.S. Dollars in accordance with the terms of the deposit agreement. Holders of ADSs may have to pay fees and expenses incurred in converting foreign currency, such as fees and expenses incurred in complying with currency exchange controls and other governmental requirements.

If the conversion of foreign currency is not practical or lawful, or if any required approvals are denied or not obtainable at a reasonable cost or within a reasonable period, the depositary may take the following actions in its discretion:

- Convert the foreign currency to the extent practical and lawful and distribute the U.S. Dollars to the holders for whom the conversion and distribution is lawful and practical.

- Distribute the foreign currency to holders for whom the distribution is lawful and practical.

- Hold the foreign currency (without liability for interest) for the applicable holders.

Governing Law/Waiver of Jury Trial

The deposit agreement, the ADRs and ADSs will be interpreted in accordance with the laws of the State of New York. The rights of holders of ordinary shares (including ordinary shares represented by ADSs) are governed by the laws of England and Wales.

AS A PARTY TO THE DEPOSIT AGREEMENT, HOLDERS OF ADSs IRREVOCABLY WAIVE THEIR RIGHT TO TRIAL BY JURY IN ANY LEGAL PROCEEDING ARISING OUT OF THE DEPOSIT AGREEMENT, THE ADRs AND ADSs AGAINST THE COMPANY AND/OR THE DEPOSITARY. If the Company or the depositary opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable in the facts and circumstances of that case in accordance with applicable case law. However, holders of ADSs will not be deemed by agreeing to the terms of the deposit agreement to have waived the Company's or the depositary's compliance with U.S. federal securities laws and the rules and regulations promulgated thereunder.

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CERTAIN CONFIDENTIAL INFORMATION MARKED BY [***] HAS BEEN EXCLUDED FROM THIS EXHIBIT BECAUSE IT IS BOTH NOT MATERIAL AND IS THE TYPE THAT THE REGISTRANT TREATS AS PRIVATE OR CONFIDENTIAL.

ORIGINALLY DATED 24 MAY 2019 AS AMENDED AND RESTATED ON 28 MAY 2021 AND ON THE SECOND EFFECTIVE DATE (AS DEFINED BELOW)

ORCHARD THERAPEUTICS PLC
as the Company

- and -

THE ENTITIES LISTED AS ORIGINAL GUARANTORS

- and -

MIDCAP FINANCIAL (IRELAND) LIMITED
as Mandated Lead Arranger

- and -

MIDCAP FINANCIAL (IRELAND) LIMITED
acting as Agent

- and -

MIDCAP FINANCIAL (IRELAND) LIMITED
acting as Security Agent

SENIOR TERM FACILITIES AGREEMENT ORIGINALLY DATED 24 MAY 2019 AS AMENDED AND RESTATED ON 28 MAY 2021 AND ON THE SECOND EFFECTIVE DATE (AS DEFINED BELOW)

Matter ref 036639/000096
F3A/SHAFEOLI/7007947

Hogan Lovells International LLP
Atlantic House, Holborn Viaduct, London EC1A 2FG

Contents

Schedules

THIS AGREEMENT is originally dated 24 May 2019 as amended and restated on 28 May 2021 and on the Second Effective Date (as defined below)

BETWEEN:

(1) **Orchard Therapeutics plc**, a company incorporated in England and Wales with company number 11494381 (the "**Company**");

(2) **The entity** listed in Part 1 of Schedule 1 (*The Original Parties*) as original borrower (the "**Original Borrower**");

(3) **The entities** listed in Part 1 of Schedule 1 (*The Original Parties*) as original guarantors (the "**Original Guarantors**");

(4) **Midcap Financial (Ireland) Limited** as mandated lead arranger (the "**Arranger**");

(5) **The Financial Institutions** listed in Part 2 of Schedule 1 (*The Original Parties*) as lenders (the "**Original Lenders**");

(6) **Midcap Financial (Ireland) Limited** as agent of the other Finance Parties (the "**Agent**"); and

(7) **Midcap Financial (Ireland) Limited** as security trustee for the Secured Parties (the "**Security Agent**").

IT IS AGREED:

SECTION 1

INTERPRETATION

1. DEFINITIONS AND INTERPRETATION

1.1 Definitions

In this Agreement:

"**2021 Fee Letter**" means the fee letter dated on or about the First Effective Date between the Agent and the Company.

"**Acceptable Bank**" means:

(a) a bank or financial institution which has a rating for its long-term unsecured and non-credit-enhanced debt obligations of BBB or higher by Standard & Poor's Rating Services or Fitch Ratings Ltd or Baa2 or higher by Moody's Investors Service Limited or a comparable rating from an internationally recognised credit rating agency; or

(b) any other bank or financial institution approved by the Agent.

"**Accession Deed**" means a document substantially in the form set out in Schedule 6 (*Form of Accession Deed*).

"**Accounting Principles**" means GAAP.

"**Additional Borrower**" means a company which becomes a Borrower in accordance with Clause 26 (*Changes to the Obligors*).

"**Additional Guarantor**" means a company which becomes a Guarantor in accordance with Clause 26 (*Changes to the Obligors*).

"**Additional Obligor**" means an Additional Borrower or an Additional Guarantor.

"**Affiliate**" means, in relation to any person: (a) a Subsidiary of that person; (b) a Holding Company of that person or any other Subsidiary of that Holding Company; or (c) in the case of a Lender, any person which controls directly or indirectly that person.

"**Agent's Spot Rate of Exchange**" means:

(a) the Agent's spot rate of exchange; or

(b) (if the Agent does not have an available spot rate of exchange) any other publicly available spot rate of exchange selected by the Agent (acting reasonably),

for the purchase of the relevant currency with the Base Currency in the London foreign exchange market at or about 11:00 am on a particular day.

"**Agreed Security Principles**" means the principles set out in Schedule 11 (*Agreed Security Principles*).

"**Annual Financial Statements**" has the meaning given to that term in Clause 21 (*Information Undertakings*).

"**Assignment Agreement**" means an agreement substantially in the form set out in Schedule 5 (*Form of Assignment Agreement*) or any other form agreed between the relevant assignor and assignee.

"**Authorisation**" means an authorisation, consent, approval, resolution, licence, exemption, filing, notarisation or registration.

"**Authority**" means any of the United Nations, the European Union, Her Majesty's Treasury, the Department for Business, Innovation and Skills or any other UK government authority, any European Union member state, or the United States government.

"**Availability Period**" means:

(a) in relation to Facility A1, the period from and including the Original Effective Date to and including the date falling two Business Days after the Original Effective Date;

(b) in relation to Facility A2, the period from and including the First Effective Date to and including the date falling two Business Days after the First Effective Date;

(c) in relation to Facility B, the period from and including 1 July 2022 to and including 1 July 2023; and

(d) in relation to Facility C, the period from and including 1 July 2023 to and including 1 July 2024.

"**Available Commitment**" means, in relation to a Facility, a Lender's Commitment under that Facility minus (subject as set out below):

(a) the amount of its participation in any outstanding Utilisations under that Facility; and

(b) in relation to any proposed Utilisation, the amount of its participation in any other Utilisations that are due to be made under that Facility on or before the proposed Utilisation Date.

"**Available Facility**" means, in relation to a Facility, the aggregate for the time being of each Lender's Available Commitment in respect of that Facility.

"**Bank Levy**" means the UK bank levy as set out in the Finance Act 2011 or any tax in any jurisdiction levied on a materially similar basis, in each case, as in force as at the Original Effective Date.

"**Base Case Model**" means the budget of the Group for the Financial Year ending on 31 December 2019.

"**Base Currency**" means US dollars.

"**Base Currency Equivalent**" means, the amount of the relevant currency required to purchase the relevant amount of the Base Currency at the Agent's Spot Rate of Exchange.

"**BLA**" means a biologics license application (as defined in the Public Health Services Act, 42 U.S.C. § 262) for authorization to introduce, or deliver for introduction, a biologic product into commerce in the U.S., or any successor application or procedure.

"**Borrower**" means an Original Borrower or an Additional Borrower unless it has ceased to be a Borrower in accordance with Clause 26 (*Changes to the Obligors*).

"**Break Costs**" means the amount (if any) by which:

(a) the interest, excluding the Margin, which a Lender should have received for the period from the date of receipt of all or any part of its participation in a Loan or Unpaid Sum to the last day of the current Interest Period in respect of that Loan or Unpaid Sum, had the principal amount or Unpaid Sum received been paid on the last day of that Interest Period;

exceeds:

(b) the amount which that Lender would be able to obtain by placing an amount equal to the principal amount or Unpaid Sum received by it on deposit with a leading bank for a period starting on the Business Day following receipt or recovery and ending on the last day of the current Interest Period.

"**Budget**" means:

(a) in relation to the period beginning on the Original Effective Date and ending on 31 December 2019, the Base Case Model to be delivered by the Company to the Agent pursuant to Clause 4.1 (*Initial conditions precedent*); and

(b) in relation to any other period, any budget delivered by the Company to the Agent in respect of that period pursuant to Clause 21.4 (*Budget*).

"**Business Day**" means a day (other than a Saturday or Sunday) on which banks are open for general business in London and New York and (in relation to the fixing of an interest rate) which is a US Government Securities Business Day.

"**Cash Equivalent Investments**" means at any time:

(a) certificates of deposit maturing within one year after the relevant date of calculation and issued by an Acceptable Bank;

(b) any investment in marketable debt obligations issued or guaranteed by the government of the United States, the United Kingdom, any member state of the European Economic Area or any Participating Member State or by an instrumentality or agency of any of them having an equivalent credit rating, maturing within one year after the relevant date of calculation and not convertible or exchangeable to any other security;

(c) commercial paper not convertible or exchangeable to any other security:

(i) for which a recognised trading market exists;

(ii) issued by an issuer incorporated in the United States, the United Kingdom, any member state of the European Economic Area or any Participating Member State;

(iii) which matures within one year after the relevant date of calculation; and

(iv) which has a credit rating of either A-1 or higher by Standard & Poor's Rating Services or F-1 or higher by Fitch Ratings Ltd or P-1 or higher by Moody's Investors Service Limited, or, if no rating is available in respect of the commercial paper, the issuer of which has, in respect of its long-term unsecured and non-credit enhanced debt obligations, an equivalent rating;

(d) Sterling bills of exchange eligible for rediscount at the Bank of England and accepted by an Acceptable Bank (or their dematerialised equivalent);

(e) any investment in money market funds which:

(i) have a credit rating of either A-1 or higher by Standard & Poor's Rating Services or F-1 or higher by Fitch Ratings Ltd or P-1 or higher by Moody's Investors Service Limited; and

(ii) invest substantially all their assets in securities of the types described in sub-paragraphs (a) to (d) above,

(iii) to the extent that investment can be turned into cash on not more than 30 days' notice;

(f) any investment made in accordance with the Investment Policy; or

(g) any other debt security approved by the Majority Lenders,

in each case, to which any member of the Group is alone (or together with other any members of the Group) beneficially entitled at that time and which is not issued or guaranteed by any member of the Group or subject to any Security (other than Security arising under the Transaction Security Documents).

"**Cash Proceeds**" means proceeds of the Charged Property which are in the form of cash.

"**Central Bank Rate**" means:

(a) the short-term interest rate target set by the US Federal Open Market Committee as published by the Federal Reserve Bank of New York from time to time; or

(b) if that target is not a single figure, the arithmetic mean of:

(i) the upper bound of the short-term interest rate target range set by the US Federal Open Market Committee and published by the Federal Reserve Bank of New York; and

(ii) the lower bound of that target range.

"**Central Bank Rate Adjustment**" means the difference (expressed as a percentage rate per annum) calculated by the Agent (or by any other Finance Party which agrees to do so in place of the Agent) between:

(a) the last available Term SOFR for the Interest Period of the relevant Loan; and

(b) the Central Bank Rate prevailing at close of business on that Business Day.

"**Change of Control**" means any person or group of persons acting in concert gains direct or indirect Control of the Company, where "**acting in concert**" means a group of persons who, pursuant to an agreement or understanding (whether formal or informal), actively co-operate, through the acquisition directly or indirectly of shares in the Company by any of them, either directly or indirectly, to obtain or consolidate control of the Company.

"**Charged Property**" means all of the assets of the Group which from time to time are, or are expressed to be, the subject of the Transaction Security.

"**Chief Financial Officer**" means the principal financial officer of the Company from time to time (or any director or officer of the Company acting as such officer's deputy in that capacity or performing those functions).

"**Closing Date**" means the date on which first Utilisation under this Agreement occurs.

"**Code**" means the US Internal Revenue Code of 1986.

"**Commitment**" means a Facility A Commitment, a Facility B Commitment or a Facility C Commitment.

"**Commodity Exchange Act**" means the Commodity Exchange Act (7 U.S.C. § 1 et seq.), as amended from time to time, and any successor statute.

"**Common Currency Amount**" means, in relation to an amount, that amount converted (to the extent not already denominated in the Base Currency) into the Base Currency at the Security Agent's Spot Rate of Exchange on the Business Day prior to the relevant calculation.

"**Company's Auditors**" means PricewaterhouseCoopers LLP or any other firm appointed by the Company to act as its statutory auditors.

"**Competitor**" means, at any time of determination, any person engaged in the same or substantially the same line of business as the Group and such business accounts for all or substantially all the revenue or net income of such person at the time of such determination.

"**Compliance Certificate**" means a certificate substantially in the form set out in Schedule 8 (*Form of Compliance Certificate*).

"**Confidential Information**" means all information relating to the Company, any Obligor, the Group, the Finance Documents or a Facility of which a Finance Party becomes aware in its capacity as, or for the purpose of becoming, a Finance Party or which is received by a Finance Party in relation to, or for the purpose of becoming a Finance Party under, the Finance Documents or a Facility from either:

(a) any member of the Group or any of its advisers; or

(b) another Finance Party, if the information was obtained by that Finance Party directly or indirectly from any member of the Group or any of its advisers,

in whatever form, and includes information given orally and any document, electronic file or any other way of representing or recording information which contains or is derived or copied from such information but excludes:

(i) information that:

(1) is or becomes public information other than as a direct or indirect result of any breach by that Finance Party of Clause 38.1 (*Confidentiality*); or

(2) is identified in writing at the time of delivery as non-confidential by any member of the Group or any of its advisers; or

(3) is known by that Finance Party before the date the information is disclosed to it in accordance with paragraphs (a) or (b) above or is lawfully obtained by that Finance Party after that date, from a source which is, as far as that Finance Party is aware, unconnected with the Group and which, in either case, as far as that Finance Party is aware, has not been obtained in breach of, and is not otherwise subject to, any obligation of confidentiality; and

(ii) any Funding Rate.

"**Confidentiality Undertaking**" means a confidentiality undertaking substantially in a recommended form of the LMA for the relevant type of proposed transaction or in any other form agreed between the Company and the Agent.

"**Constitutional Documents**" means the constitutional documents of the Company.

"**Contribution Notice**" means a contribution notice issued by the Pensions Regulator under section 38 or section 47 of the Pensions Act 2004.

"**Control**" means:

(a) the power (whether by way of ownership of shares, proxy, contract, agency or otherwise) to:

(i) cast, or control the casting of, more than 50% of the maximum number of votes that might be cast at a general meeting of an entity;

(ii) appoint or remove all, or the majority, of the directors or other equivalent officers of an entity; or

(iii) give directions with respect to the operating and financial policies of an entity with which the directors or other equivalent officers of that entity are obliged to comply; or

(b) the holding beneficially of more than 50% of the issued share capital of an entity (excluding any part of that issued share capital that carries no right to participate beyond a specified amount in a distribution of either profits or capital).

"**Credit Adjustment Spread**" means 0.10 per cent. per annum.

"**CTA**" means the Corporation Tax Act 2009.

"**Declared Default**" means: (a) an Event of Default in respect of which the Agent has exercised any of its rights under Clause 24.18 (*Acceleration*); or (b) in relation to any US Obligor, automatic acceleration pursuant to (i) Clause 24.19 (*Acceleration for US insolvency proceedings*) of this Agreement as a result of an Event of Default by such US Obligor under Clause 24.17 (*US insolvency proceedings*) of this Agreement.

"**Default**" means an Event of Default or any event or circumstance specified in Clause 24 (*Events of Default*) which would (with the expiry of a grace period, the giving of notice, the making of any determination under the Finance Documents or any combination of any of the foregoing) be an Event of Default.

"**Defaulting Lender**" means any Lender:

(a) which has failed to make its participation in a Loan available or has notified the Agent or the Company (which has notified the Agent) that it will not make its participation in a Loan available by the Utilisation Date of that Loan in accordance with Clause 5.4 (*Lenders' participation*) or which has failed to provide cash collateral;

(b) which has otherwise rescinded or repudiated a Finance Document; or

(c) with respect to which a Finance Party Insolvency Event has occurred and is continuing,

unless, in the case of paragraph (a):

(i) its failure to pay is caused by:

(1) administrative or technical error; or

(2) a Disruption Event; and

payment is made within 5 Business Days of its due date; or

(ii) the Lender is disputing in good faith whether it is contractually obliged to make the payment in question.

"**Delegate**" means any delegate, agent, attorney or co-trustee appointed by the Security Agent.

"**Designated Parties List**" means the Specially Designated Nationals List, the Sectoral Sanctions Identifications List and the Foreign Sanctions Evaders List maintained by the Office of Foreign Assets Control of the US Department of the Treasury, or any similar list of sanctioned persons or entities maintained by any Authority.

"**Disposal**" has the meaning given to that term in Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*).

"**Disruption Event**" means either or both of:

(a) a material disruption to those payment or communications systems or to those financial markets which are, in each case, required to operate in order for payments to be made in connection with the Facilities (or otherwise in order for the transactions contemplated by the Finance Documents to be carried out) which disruption is not caused by, and is beyond the control of, any of the Parties; or

(b) the occurrence of any other event which results in a disruption (of a technical or systems-related nature) to the treasury or payments operations of a Party preventing that, or any other Party:

(i) from performing its payment obligations under the Finance Documents; or

(ii) from communicating with other Parties in accordance with the terms of the Finance Documents,

and which (in either such case) is not caused by, and is beyond the control of, the Party whose operations are disrupted.

"**Dormant Subsidiary**" means a member of the Group which is not an Obligor and does not:

(a) own, legally or beneficially, gross assets (including indebtedness owed to it) which in aggregate have a value of $10,000,000 or more (or its Base Currency Equivalent); or

(b) have liabilities in excess of $10,000,000 (or its Base Currency Equivalent).

"**Eligible Institution**" means any Lender or other bank, financial institution, trust, fund or other entity selected by the Company and which, in each case, is not a member of the Group.

"**EMA**" means the European Medicines Agency and any successor agency thereof.

"**Environment**" means humans, animals, plants and all other living organisms including the ecological systems of which they form part and the following media:

(a) air (including, without limitation, air within natural or man-made structures, whether above or below ground);

(b) water (including, without limitation, territorial, coastal and inland waters, water under or within land and water in drains and sewers); and

(c) land (including, without limitation, land under water).

"**Environmental Claim**" means any claim, proceeding, formal notice or investigation by any person in respect of any Environmental Law.

"**Environmental Law**" means any applicable law or regulation which relates to:

(a) the pollution or protection of the Environment;

(b) the conditions of the workplace; or

(c) the generation, handling, storage, use, release or spillage of any substance which, alone or in combination with any other, is capable of causing harm to the Environment, including, without limitation, any waste.

"**Environmental Permits**" means any permit or other Authorisation or the filing of any notification, report or assessment required under any Environmental Law for the operation of the business of any member of the Group conducted on or from the properties owned or used by any member of the Group.

"**ERISA**" means the United States Employee Retirement Income Security Act of 1974, as amended from time to time, and the regulations promulgated and the rulings issued thereunder;

"**ERISA Affiliate**" means any person treated as a single employer with any Obligor for the purpose of sections 414(b), (c), (m) or (o) of the Code.

"**ERISA Event**" means:

(a) a reportable event specified as such in Section 4043 of ERISA and the regulations issued thereunder with respect to any Plan, other than an event in relation to which the requirement to give notice of that event is waived by any regulation;

(b) the failure to meet the minimum funding standard under sections 412 of the Code with respect to any Plan, whether or not waived in accordance with Section 412(c) of the Code;

(c) the provision by the administrator of any Plan pursuant to Section 4041(a)(2) of ERISA of a notice of intent to terminate such Plan in a distress termination described in Section 4041(c) of ERISA;

(d) the institution of proceedings under Section 4042 of ERISA by the PBGC for the termination of, or the appointment of a trustee to administer, any Plan;

(e) the incurrence of any liability under Title IV of ERISA with respect to the termination of any Plan or withdrawal from any Plan (other than premiums due and not delinquent under Section 4007 of ERISA);

(f) the incurrence by any Obligor or any of its ERISA Affiliates of any liability with respect to the withdrawal or partial withdrawal from any Multiemployer Plan;

(g) the receipt by any Obligor or any ERISA Affiliate of any notice that a Multiemployer Plan is insolvent or in reorganisation, within the meaning of Title IV of ERISA; or

(h) the determination that any Plan is in "at risk status" (within the meaning of Section 430 of the Code and Section 303 of ERISA);

(i) the requirement that a Plan provide security pursuant to Section 436(f) of the Code;

(j) engagement in a "prohibited transaction" within the meaning of Section 406 of ERISA and Section 4975 of the Code with respect to any Plan; or

(k) the institution of a proceeding by a fiduciary of any Multiemployer Plan to enforce Section 515 of ERISA which proceeding is not dismissed within 30 days.

"**Excluded Account**" has the meaning given to that term in the New York law Transaction Security Documents.

"**Excluded Swap Obligation**" means, with respect to any Obligor, any Swap Obligation if, and to the extent that, all or a portion of the guaranty of such Obligor of (including by virtue of the joint and several liability provisions contained herein), or the grant by such Obligor of a security interest to secure, such Swap Obligation (or any guaranty thereof) is or becomes illegal under the Commodity Exchange Act or any rule, regulation or order of the Commodity Futures Trading Commission (or the application or official interpretation of any thereof) by virtue of such Obligor's failure for any reason to constitute an "eligible contract participant" as defined in the Commodity Exchange Act and the regulations thereunder at the time the guaranty of such Obligor or the grant of such security interest becomes effective with respect to such Swap Obligation. If a Swap Obligation arises under a master agreement governing more than one swap, such exclusion shall apply only to the portion of such Swap Obligation that is attributable to swaps for which such guaranty or security interest is or becomes illegal.

"**Event of Default**" means any event or circumstance specified as such in Clause 24 (*Events of Default*).

"**Facility**" means Facility A, Facility B or Facility C.

"**Facility A**" means the term loan facility made available under this Agreement as described in sub-paragraphs (a) and (b) of Clause 2.1 (*The Facilities*), and consisting of Facility A1 and Facility A2.

"**Facility A Commitment**" means a Facility A1 Commitment and/or a Facility A2 Commitment.

"**Facility A Loan**" means a Facility A1 Loan and/or a Facility A2 Loan.

"**Facility A1**" means the tranche of Facility A which is made available by those Lenders with a Facility A1 Commitment.

"**Facility A1 Commitment**" means:

(a) in relation to an Original Lender, the amount in the Base Currency set opposite its name under the heading "**Facility A1 Commitment**" in Part 2 of Schedule 1 (*The Original Parties*) and the amount in the Base Currency of any other Facility A1 Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*); and

(b) in relation to any other Lender, the amount in the Base Currency of any Facility A1 Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*),

to the extent not cancelled, reduced or transferred by it under this Agreement.

"**Facility A1 Loan**" means a loan made or to be made under Facility A1 or the principal amount outstanding for the time being of that loan.

"**Facility A2**" means the tranche of Facility A which is made available by those Lenders with a Facility A2 Commitment.

"**Facility A2 Commitment**" means:

(a) in relation to an Original Lender, the amount in the Base Currency set opposite its name under the heading "**Facility A2 Commitment**" in Part 2 of Schedule 1 (*The*

Original Parties) and the amount in the Base Currency of any other Facility A2 Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*); and

(b) in relation to any other Lender, the amount in the Base Currency of any Facility A2 Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*),

to the extent not cancelled, reduced or transferred by it under this Agreement.

"**Facility A2 Loan**" means a loan made or to be made under Facility A2 or the principal amount outstanding for the time being of that loan.

"**Facility B**" means the term loan facility made available under this Agreement as described in sub-paragraph (c) of Clause 2.1 (*The Facilities*).

"**Facility B Commitment**" means:

(a) in relation to an Original Lender, the amount in the Base Currency set opposite its name under the heading "Facility B Commitment" in Part 2 of Schedule 1 (*The Original Parties*) and the amount in the Base Currency of any other Facility B Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*); and

(b) in relation to any other Lender, the amount in the Base Currency of any Facility B Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*),

to the extent not cancelled, reduced or transferred by it under this Agreement.

"**Facility B Loan**" means a loan made or to be made under Facility B or the principal amount outstanding for the time being of that loan.

"**Facility C**" means the term loan facility made available under this Agreement as described in sub-paragraph (d) of Clause 2.1 (*The Facilities*).

"**Facility C Commitment**" means:

(a) in relation to an Original Lender, the amount in the Base Currency set opposite its name under the heading "Facility C Commitment" in Part 2 of Schedule 1 (*The Original Parties*) and the amount in the Base Currency of any other Facility C Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*); and

(b) in relation to any other Lender, the amount in the Base Currency of any Facility C Commitment transferred to it under this Agreement or assumed by it in accordance with Clause 2.2 (*Increase*),

to the extent not cancelled, reduced or transferred by it under this Agreement.

"**Facility C Loan**" means a loan made or to be made under Facility C or the principal amount outstanding for the time being of that loan.

"**Facility Office**" means:

(a) in respect of a Lender, the office or offices notified by that Lender to the Agent in writing on or before the date it becomes a Lender (or, following that date, by not less than five Business Days' written notice) as the office or offices through which it will perform its obligations under this Agreement; or

(b) in respect of any other Finance Party, the office in the jurisdiction in which it is resident for tax purposes.

"**FATCA**" means:

(a) sections 1471 to 1474 of the Code or any associated regulations; or

(b) any treaty, law or regulation of any other jurisdiction, or relating to an intergovernmental agreement between the US and any other jurisdiction, which (in either case) facilitates the implementation of any law or regulation referred to in paragraph (a) above; or

(c) any agreement pursuant to the implementation of any treaty, law or regulation referred to in paragraphs (a) or (b) above with the US Internal Revenue Service, the US government or any governmental or taxation authority in any other jurisdiction.

"**FATCA Application Date**" means:

(a) in relation to a "withholdable payment" described in section 1473(1)(A)(i) of the Code (which relates to payments of interest and certain other payments from sources within the US), 1 July 2014; or

(b) in relation to a "passthru payment" described in section 1471(d)(7) of the Code not falling within paragraph (a) above, the first date from which such payment may become subject to a deduction or withholding required by FATCA.

"**FATCA Deduction**" means a deduction or withholding from a payment under a Finance Document required by FATCA.

"**FATCA Exempt Party**" means a Party that is entitled to receive payments free from any FATCA Deduction.

"**FDA**" means the Food and Drug Administration of the United States, any comparable state, provincial or local governmental authority or regulator, and any successor agency of any of the foregoing.

"**FDCA**" means the Federal Food, Drug and Cosmetic Act, as amended, 21 U.S.C. Section 301 *et seq.*, and all regulations promulgated thereunder.

"**Fee Letter**" means:

(a) any letter or letters dated on or about Original Effective Date between the Arranger and the Company (or the Agent and the Company or the Security Agent and the Company) setting out any of the fees referred to in Clause 13 (*Fees*);

(b) the 2021 Fee Letter; and

(c) any agreement setting out fees payable to a Finance Party referred to in paragraph (f) of Clause 2.2 (*Increase*).

"**Finance Document**" means this Agreement, the First Amendment and Restatement Agreement, the Second Amendment and Restatement Agreement, any Accession Deed, any Compliance Certificate, any Fee Letter, any Resignation Letter, any Selection Notice, any Transaction Security Document, any Utilisation Request and any other document designated as a "Finance Document" by the Agent and the Company.

"**Finance Lease**" means any lease or hire purchase contract, a liability under which would, in accordance with the Accounting Principles, be treated as a balance sheet liability.

"**Finance Party**" means the Agent, the Arranger, the Security Agent or a Lender.

"**Finance Party Insolvency Event**" in relation to an entity means that the entity:

(a) is dissolved (other than pursuant to a consolidation, amalgamation or merger);

(b) becomes insolvent or is unable to pay its debts or fails or admits in writing its inability generally to pay its debts as they become due;

(c) makes a general assignment, arrangement or composition with or for the benefit of its creditors;

(d) institutes or has instituted against it, by a regulator, supervisor or any similar official with primary insolvency, rehabilitative or regulatory jurisdiction over it in the jurisdiction of its incorporation or organisation or the jurisdiction of its head or home office, a proceeding seeking a judgment of insolvency or bankruptcy or any other relief under any bankruptcy or insolvency law or other similar law affecting creditors' rights, or a petition is presented for its winding-up or liquidation by it or such regulator, supervisor or similar official;

(e) has instituted against it a proceeding seeking a judgment of insolvency or bankruptcy or any other relief under any bankruptcy or insolvency law or other similar law affecting creditors' rights, or a petition is presented for its winding-up or liquidation, and, in the case of any such proceeding or petition instituted or presented against it, such proceeding or petition is instituted or presented by a person or entity not described in paragraph (d) above and:

(i) results in a judgment of insolvency or bankruptcy or the entry of an order for relief or the making of an order for its winding-up or liquidation; or

(ii) is not dismissed, discharged, stayed or restrained in each case within 30 days of the institution or presentation thereof;

(f) has exercised in respect of it one or more of the stabilisation powers pursuant to Part 1 of the Banking Act 2009 and/or has instituted against it a bank insolvency proceeding pursuant to Part 2 of the Banking Act 2009 or a bank administration proceeding pursuant to Part 3 of the Banking Act 2009;

(g) has a resolution passed for its winding-up, official management or liquidation (other than pursuant to a consolidation, amalgamation or merger);

(h) seeks or becomes subject to the appointment of an administrator, provisional liquidator, conservator, receiver, trustee, custodian or other similar official for it or for all or substantially all its assets (other than, for so long as it is required by law or regulation not to be publicly disclosed, any such appointment which is to be made, or is made, by a person or entity described in paragraph (d) above);

(i) has a secured party take possession of all or substantially all its assets or has a distress, execution, attachment, sequestration or other legal process levied, enforced or sued on or against all or substantially all its assets and such secured party maintains possession, or any such process is not dismissed, discharged, stayed or restrained, in each case within 30 days thereafter;

(j) causes or is subject to any event with respect to it which, under the applicable laws of any jurisdiction, has an analogous effect to any of the events specified in paragraphs (a) to (i) above; or

(k) takes any action in furtherance of, or indicating its consent to, approval of, or acquiescence in, any of the foregoing acts.

"**Financial Indebtedness**" means any indebtedness for or in respect of:

(a) moneys borrowed and debit balances at banks or other financial institutions;

(b) any acceptance under any acceptance credit or bill discounting facility or dematerialised equivalent;

(c) any note purchase facility or the issue of bonds (but not Trade Instruments), notes, debentures, loan stock or any similar instrument;

(d) the amount of any liability in respect of Finance Leases;

(e) receivables sold or discounted (other than any receivables to the extent they are sold on a non-recourse basis);

(f) any Treasury Transaction (and, when calculating the value of that Treasury Transaction, only the marked to market value (or, if any actual amount is due as a result of the termination or close-out of that Treasury Transaction, that amount) shall be taken into account);

(g) any counter-indemnity obligation in respect of a guarantee, bond, standby or documentary letter of credit or any other instrument issued by a bank or financial institution in respect of:

(i) an underlying liability (but not, in any case, Trade Instruments) of an entity which is not a member of the Group which liability would fall within one of the other paragraphs of this definition; or

(ii) any liabilities of any member of the Group relating to any post-retirement benefit scheme;

(h) any amount raised by the issue of shares which are redeemable (other than at the option of the issuer) before the Termination Date or are otherwise classified as borrowings under the Accounting Principles;

(i) any amount raised under any other transaction (including any forward sale or purchase, sale and sale back or sale and leaseback agreement) having the commercial effect of a borrowing or otherwise classified as borrowings under the Accounting Principles; and

(j) the amount of any liability in respect of any guarantee for any of the items referred to in paragraphs (a) to (i) above.

"**Financial Quarter**" means the period commencing on the day after one Quarter Date and ending on the next Quarter Date.

"**Financial Support Direction**" means a financial support direction issued by the Pensions Regulator under Section 43 of the Pensions Act 2004.

"**Financial Year**" means the annual accounting period of the Group ending on or about 31 December in each year.

"**First Amendment and Restatement Agreement**" means the amendment and restatement agreement amending and restating this Agreement and made between, amongst others, the Company, the Agent and the Security Agent dated 28 May 2021.

"**First Effective Date**" means 28 May 2021.

"**Funding Rate**" means any individual rate notified by a Lender to the Agent pursuant to paragraph (a)(ii) of Clause 12.3 (*Cost of funds*).

"**GAAP**" means generally accepted accounting principles in the United States as at the Original Effective Date.

"**Group**" means the Company and each of its Subsidiaries for the time being.

"**Group Structure Chart**" means the group structure chart showing the Group as at the Original Effective Date.

"**Group Unrestricted Cash**" means cash and Cash Equivalent Investments made pursuant to the Investment Policy of the Group that:

(a) are subject to a first priority perfected Security in favour of Security Agent and that are not subject to any other Security (other than Permitted Security);

(b) are held in a bank account which satisfies the requirements of Section 9.1 of the Agreed Security Principals; and

(c) are not funds for the payment of a drawn or committed but unpaid draft, ACH or EFT transaction.

"**Guarantor**" means an Original Guarantor or an Additional Guarantor unless it has ceased to be a Guarantor in accordance with Clause 26 (*Changes to the Obligors*).

"**Holding Company**" means, in relation to a person, any other person in respect of which it is a Subsidiary.

"**Impaired Agent**" means the Agent at any time when:

(a) it has failed to make (or has notified a Party that it will not make) a payment required to be made by it under the Finance Documents by the due date for payment;

(b) the Agent otherwise rescinds or repudiates a Finance Document;

(c) (if the Agent is also a Lender) it is a Defaulting Lender under paragraph (a), (b) or (c) of the definition of "Defaulting Lender"; or

(d) a Finance Party Insolvency Event has occurred and is continuing with respect to the Agent;

unless, in the case of paragraph (a) above:

(i) its failure to pay is caused by:

(1) administrative or technical error; or

(2) a Disruption Event; and

payment is made within 5 Business Days of its due date; or

(ii) the Agent is disputing in good faith whether it is contractually obliged to make the payment in question.

"**Increase Confirmation**" means a confirmation substantially in the form set out in Schedule 10 (*Form of Increase Confirmation*).

"**Increase Lender**" has the meaning given to that term in Clause 2.2 (*Increase*).

"**Intellectual Property**" means:

(a) any patents, trademarks, service marks, designs, business names, copyrights, database rights, design rights, domain names, moral rights, inventions, confidential information, knowhow and other intellectual property rights and interests (which may now or in the future subsist), whether registered or unregistered; and

(b) the benefit of all applications and rights to use such assets of each member of the Group (which may now or in the future subsist).

"**Interest Period**" means, in relation to a Loan, each period determined in accordance with Clause 11 (*Interest Periods*) and, in relation to an Unpaid Sum, each period determined in accordance with Clause 10.3 (*Default interest*).

"**Interpolated Term SOFR**" means, in relation to any Loan, the rate which results from interpolating on a linear basis between:

(a) either:

(i) the applicable Term SOFR (as of the Specified Time) for the longest period (for which Term SOFR is available) which is less than the Interest Period of that Loan; or

(ii) if no such Term SOFR is available for a period which is less than the Interest Period of that Loan, one-month Term SOFR (as of the Specified Time); and

(b) the applicable Term SOFR (as of the Specified Time) for the shortest period (for which Term SOFR is available) which exceeds the Interest Period of that Loan,

each as of the Specified Time for the currency of that Loan.

"**ITA**" means the Income Tax Act 2007.

"**Investment Policy**" means the investment policy of the Obligors dated 7 February 2018, as amended from time to time by the Obligors.

"**Joint Venture**" means any joint venture entity, whether a company, unincorporated firm, undertaking, association, joint venture or partnership or any other entity.

"**Lead Product**" means [***].

"**Legal Opinion**" means any legal opinion delivered to the Agent under Clause 4.1 (*Initial conditions precedent*) or Clause 26 (*Changes to the Obligors*).

"**Legal Reservations**" means:

(a) the principle that equitable remedies may be granted or refused at the discretion of a court and the limitation of enforcement by laws relating to insolvency, reorganisation and other laws generally affecting the rights of creditors;

(b) the time barring of claims under the Limitation Acts, the possibility that an undertaking to assume liability for or indemnify a person against non-payment of UK stamp duty may be void and defences of set-off or counterclaim; and

(c) similar principles, rights and defences under the laws of any Relevant Jurisdiction.

"**Lender**" means:

(a) any Original Lender; and

(b) any bank, financial institution, trust, fund or other entity which has become a Party as a "Lender" in accordance with Clause 2.2 (*Increase*) or Clause 25 (*Changes to the Lenders*),

which in each case has not ceased to be a Party as such in accordance with the terms of this Agreement.

"**Lien**" means, with respect to any asset, any mortgage, leasehold mortgage, lien, pledge, charge, security interest, hypothecation, or encumbrance of any kind in respect of such asset. For the purposes of this Agreement, Person shall be deemed to own any asset subject to a Lien which it has acquired or holds subject to the interest of a vendor or lessor under any conditional sale agreement, capital lease obligation or other title retention agreement relating to such asset.

"**Limitation Acts**" means the Limitation Act 1980 and the Foreign Limitation Periods Act 1984.

"**LMA**" means the Loan Market Association.

"**Loan**" means a Facility A Loan, a Facility B Loan or a Facility C Loan.

"**Majority Lenders**" means a Lender or Lenders whose Commitments aggregate more than 66⅔ per cent. of the Total Commitments (or, if the Total Commitments have been reduced to zero, aggregated more than 66⅔ per cent. of the Total Commitments immediately prior to that reduction).

"**Market Disruption Rate**" means the percentage rate per annum which is the aggregate of the Reference Rate and the Credit Adjustment Spread.

"**Marketing Authorization Application**" means [***].

"**Margin**" means:

(a) in relation to any Facility A Loan 5.95 per cent per annum;

(b) in relation to any Facility B Loan 5.95 per cent per annum; and

(c) in relation to any Facility C Loan 5.95 per cent per annum.

"**Material Adverse Effect**" means a material adverse effect on:

(a) the business, operations, property or condition (financial or otherwise) of the Group taken as a whole; or

(b) the ability of the Obligors to perform their payment obligations under the Finance Documents; or

(c) the validity or enforceability of, or the effectiveness or ranking of any Security granted or purporting to be granted pursuant to any of, the Finance Documents.

"**Month**" means a period starting on one day in a calendar month and ending on the numerically corresponding day in the next calendar month, except that:

(a) (subject to paragraph (c) below) if the numerically corresponding day is not a Business Day, that period shall end on the next Business Day in that calendar month in which that period is to end if there is one, or if there is not, on the immediately preceding Business Day;

(b) if there is no numerically corresponding day in the calendar month in which that period is to end, that period shall end on the last Business Day in that calendar month; and

(c) if an Interest Period begins on the last Business Day of a calendar month, that Interest Period shall end on the last Business Day in the calendar month in which that Interest Period is to end.

The above rules will only apply to the last Month of any period.

"**Monthly Cash Burn Amount**" means an amount equal to the Group's change in cash and Cash Equivalent Investments, without giving effect to any increase resulting from contributions or proceeds of financings, for either:

(a) the six month period ending on the last day of the month immediately preceding the proposed completion of the Permitted Acquisition and based upon the financial statements delivered to Agent in accordance with this Agreement for such period; or

(b) the six month period immediately following the six month period referred to in paragraph (a) above and based upon the Transaction Projections (as defined in the definition of "Permitted Acquisition"),

using whichever calculation as between clause (a) and clause (b) demonstrates a higher burn rate (or, in other words, more cash used), in either case, divided by six.

"**Multiemployer Plan**" means a "multiemployer plan" within the meaning of Section 4001(a)(3) of ERISA which is covered by Title IV of ERISA and which is contributed to (or to which there is an obligation to contribute) by any Obligor or ERISA Affiliate.

“**Net Revenue**” means, for any period, the consolidated revenue of Obligors for such period, as determined in accordance with GAAP; provided that in no event shall Net Revenue include any upfront or milestone payments or similar non-recurring payment

received by Obligors in connection with any out-bound license agreement or other commercial contract.

"**New Lender**" has the meaning given to that term in Clause 25 (*Changes to the Lenders*).

"**Non-US Subsidiary**" means any direct or indirect Subsidiary that is not organised under the laws of the United States or any state or territory thereof or the District of Columbia.

"**Obligations**" means all present and future obligations and liabilities (whether actual or contingent and whether owed jointly, severally or in any other capacity whatsoever) of the Obligors to the Finance Parties (or any of them) under the Finance Documents.

"**Obligor**" means the Company, the Borrower or a Guarantor.

"**Obligors' Agent**" means the Company, appointed to act on behalf of each Obligor in relation to the Finance Documents pursuant to Clause 2.4 (*Obligors' Agent*).

"**Original Effective Date**" means 24 May 2019.

"**Original Financial Statements**" means:

(a) the audited consolidated financial statements of the Company for the Financial Year ended 31 December 2018; and

(b) in relation to any other Obligor, its audited financial statements delivered to the Agent as required by Clause 26 (*Changes to the Obligors*).

"**Original Jurisdiction**" means, in relation to an Obligor, the jurisdiction under whose laws that Obligor is incorporated as at the Original Effective Date or, in the case of an Additional Obligor, as at the date on which that Additional Obligor becomes Party as a Borrower or a Guarantor (as the case may be).

"**Original Obligor**" means the Original Borrower or an Original Guarantor.

"**[***]**" means **[***]**.

"**[***]**" means **[***]**.

"**[***]**" means **[***]**.

"**[***]**" means **[***]**.

"**[***]**" means **[***]**.

"**[***]**" means **[***]**.

"**Participating Member State**" means any member state of the European Union that adopts or has adopted the euro as its lawful currency in accordance with legislation of the European Union relating to Economic and Monetary Union.

"**Party**" means a party to this Agreement.

"**PBGC**" means the United States Pension Benefit Guaranty Corporation or any successor to it.

"**Pensions Regulator**" means the body corporate called the Pensions Regulator established under Part 1 of the Pensions Act 2004.

"**Permitted Acquisition**" means:

(a) an acquisition by a member of the Group of an asset sold, leased, transferred or otherwise disposed of by another member of the Group in circumstances constituting a Permitted Disposal;

(b) an acquisition of shares or securities pursuant to a Permitted Share Issue;

(c) an acquisition of securities which are Cash Equivalent Investments so long as, in the case of an Obligor, those Cash Equivalent Investments become subject to the Transaction Security as soon as is reasonably practicable;

(d) the acquisition of stock in trade in the ordinary course of trading on arm's length terms (for the avoidance of doubt, excluding the acquisition (including through licensing) of any Product, Product line or Intellectual Property of or from any other person);

(e) the incorporation of a company which on incorporation becomes a member of the Group, but only if:

(i) that company is incorporated in the European Union, the United Kingdom or the United States with limited liability; and

(ii) if the shares in the company are owned by an Obligor, Security over the shares of that company, in form and substance satisfactory to the Agent, is created in favour of the Security Agent within 30 days of the date of its incorporation;

(f) an acquisition (not being an acquisition by the Company), for cash consideration, (i) of all of the issued share capital of a limited liability company; (ii) of (if the acquisition is made by a limited liability company whose sole purpose is to make the acquisition) a business or undertaking carried on as a going concern; or (iii) (including through licensing) of any Product, Product line or Intellectual Property of or from any other person, but, in each case, only if:

(i) no Event of Default is continuing on the closing date for the acquisition or would occur as a result of the acquisition;

(ii) in the case of the acquisition of a company, business or undertaking, the acquired company, business or undertaking is incorporated or established, and carries on its principal business in the European Union, the United Kingdom or the United States and is engaged in a business substantially the same as or complementary to that carried on by the Group; and

(iii) in the case of an acquisition of a company, the acquired company becomes an Additional Guarantor and grants Transaction Security in accordance with Clause 26.2 (*Additional Guarantors*) within 30 days following the date of completion of the acquisition; and

(g) any acquisition with the prior consent of the Majority Lenders.

"**Permitted Disposal**" means (apart from any transaction involving shares in any member of the Group, which is not a Permitted Disposal in any circumstances) any sale, lease, licence, surrender, transfer or other disposal which, except in the case of paragraph (c), is on arm's length terms:

(a) of trading stock or cash made by any member of the Group in the ordinary course of business of the disposing entity;

(b) of any Intellectual Property that does not relate to a Lead Product;

(c) of any asset by a member of the Group (the "**Disposing Company**") to another member of the Group (the "**Acquiring Company**"), but if:

(i) the Disposing Company is an Obligor, the Acquiring Company must also be an Obligor;

(ii) the Disposing Company had given Security over the asset, the Acquiring Company must give equivalent Security over that asset; and

(iii) the Disposing Company is a Guarantor, the Acquiring Company must be a Guarantor guaranteeing at all times an amount no less than that guaranteed by the Disposing Company;

(d) of tangible assets which are not expressed to be subject to a fixed charge, in exchange for other tangible assets comparable or superior as to type, value and quality;

(e) of obsolete, surplus or redundant tangible assets on arm's length terms which are not required for the efficient operation of its business;

(f) of Cash Equivalent Investments for cash or in exchange for other Cash Equivalent Investments;

(g) so long as no Default or Event of Default has occurred and is continuing (or would result from such transaction), of cash or Cash Equivalent Investments to a Permitted Joint Venture, to the extent permitted by Clause 23.12 (*Joint Ventures*);

(h) arising as a result of any Permitted Security;

(i) to which the Majority Lenders have given their prior written consent (and this may include consent to a transaction including shares in any member of the Group); and

(j) so long as no Default or Event of Default has occurred and is continuing (or would result from such transaction), of tangible assets (other than the disposal or exclusive licence of Intellectual Property) for cash where the higher of the market value and net consideration receivable (when aggregated with the higher of the market value and net consideration receivable for any other sale, lease, licence, transfer or other disposal not allowed under the preceding paragraphs or as a Permitted Transaction) does not exceed $2,500,000 (or its equivalent) in any Financial Year of the Company.

"**Permitted Distribution**" means:

(a) the payment of a dividend to the Company or any of its wholly-owned Subsidiaries;

(b) dividends payable solely in common stock; and

(c) repurchases of stock of former employees, directors or consultants pursuant to stock purchase agreements so long as an Event of Default is not continuing at the time of such repurchase and would not occur after giving effect to such repurchase,

provided, however, that such repurchase does not exceed $2,500,000 (or its equivalent) in any Financial Year of the Company.

"**Permitted Financial Indebtedness**" means Financial Indebtedness:

(a) arising under a foreign exchange transaction for spot or forward delivery entered into in connection with protection against fluctuation in currency rates where that foreign exchange exposure arises in the ordinary course of trade, but not a foreign exchange transaction for investment or speculative purposes;

(b) arising under a letter of credit, guarantee or indemnity, overdraft or credit card facility provided that the outstanding amount does not exceed $10,000,000 (or its Base Currency Equivalent) in aggregate for the Group at any time;

(c) arising under a Permitted Loan or a Permitted Guarantee or as permitted by Clause 23.31 (*Treasury Transactions*);

(d) under Finance Leases of vehicles, plant, equipment or computers, provided that the aggregate capital value of all such items so leased under outstanding leases by members of the Group does not exceed $10,000,000 (or its Base Currency Equivalent) at any time; and

(e) not permitted by the preceding paragraphs or as a Permitted Transaction and the outstanding amount of which does not exceed $5,000,000 (or its Base Currency Equivalent) in aggregate for the Group at any time.

"**Permitted Guarantee**" means:

(a) the endorsement of negotiable instruments in the ordinary course of trade;

(b) any performance or similar bond guaranteeing performance by a member of the Group under any contract entered into in the ordinary course of trade;

(c) any guarantee of a Joint Venture to the extent permitted by Clause 23.12 (*Joint Ventures*);

(d) any guarantee of Permitted Financial Indebtedness which is referred to in the definition of, or otherwise constitutes, Permitted Financial Indebtedness except under paragraph (d) of that definition;

(e) any guarantee of a Permitted Loan, provided that no Obligor shall guarantee the Financial Indebtedness of any member of the Group which is not an Obligor unless the amount of the relevant guaranteed obligation is within the de minimis threshold in paragraph (e) of the definition of "Permitted Loan" at all times;

(f) any guarantee given in respect of the netting or set-off arrangements permitted pursuant to paragraph (b) of the definition of "Permitted Security";

(g) any indemnity given in the ordinary course of the documentation of an acquisition or disposal transaction which is a Permitted Acquisition or Permitted Disposal which indemnity is in a customary form and subject to customary limitations; and

(h) guarantees not otherwise permitted by the preceding paragraphs, the aggregate principal outstanding amount guaranteed by which (when aggregated with all such

other guarantees and with any Financial Indebtedness incurred by the Group) does not exceed $2,500,000 at any time.

"**Permitted Joint Venture**" means any cash investment in any Joint Venture where:

(a) the Joint Venture is incorporated, or established, and carries on its principal business in the European Union, the United Kingdom or the United States and is a vehicle incorporated with limited liability;

(b) the Joint Venture is engaged in a business substantially the same as, or complementary to that carried on by the Group; and

(c) in any Financial Year of the Company, the aggregate of:

(i) all amounts subscribed for shares in, lent to, or invested in all such Joint Ventures by any member of the Group;

(ii) the contingent liabilities of any member of the Group under any guarantee given in respect of the liabilities of any such Joint Venture; and

(iii) the market value of any cash or Cash Equivalent Investments transferred by any member of the Group to any such Joint Venture,

does not exceed $10,000,000 (or its Base Currency Equivalent) in any Financial Year of the Company.

"**Permitted Loan**" means:

(a) any trade credit extended by any member of the Group to its customers on normal commercial terms and in the ordinary course of its trading activities;

(b) Financial Indebtedness which is referred to in the definition of, or otherwise constitutes, Permitted Financial Indebtedness except under paragraph (d) of that definition;

(c) a loan made to a Joint Venture to the extent permitted under Clause 28.11 (*Joint Ventures*);

(d) a loan made by an Obligor to another Obligor or made by a member of the Group which is not an Obligor to another member of the Group;

(e) any loan made by an Obligor to a member of the Group which is not an Obligor so long as the aggregate amount of the Financial Indebtedness under any such loans does not exceed $250,000 (or its equivalent) at any time;

(f) a loan made by a member of the Group to an employee or director of any member of the Group if the amount of that loan when aggregated with the amount of all loans to employees and directors by members of the Group does not exceed $250,000 (or its equivalent) at any time; and

(g) any loan (other than a loan made by a member of the Group to another member of the Group) so long as the aggregate amount of Financial Indebtedness under any such loans does not exceed $250,000 (or its equivalent) at any time,

so long as in the case of paragraphs (d) and (e) above the creditor of such Financial Indebtedness shall (if it is an Obligor) grant security over its rights in respect of such

Financial Indebtedness in favour of the Secured Parties on terms acceptable to the Agent (acting on the instructions of the Majority Lenders).

"**Permitted Security**" means:

(a) any lien arising by operation of law and in the ordinary course of trading and not as a result of any default or omission by any member of the Group;

(b) any netting or set-off arrangement entered into by any member of the Group in the ordinary course of its banking arrangements for the purpose of netting debit and credit balances of members of the Group;

(c) any payment or close out netting or set-off arrangement pursuant to any Treasury Transaction or foreign exchange transaction entered into by a member of the Group which constitutes Permitted Financial Indebtedness, excluding any Security or Quasi-Security under a credit support arrangement;

(d) to the extent such Security relates to, or is granted in support of facilities permitted pursuant to paragraph (b) of "Permitted Financial Indebtedness";

(e) any Security or Quasi-Security over or affecting any asset acquired by a member of the Group after the Original Effective Date if:

(i) the Security or Quasi-Security was not created in contemplation of the acquisition of that asset by a member of the Group;

(ii) the principal amount secured has not been increased in contemplation of or since the acquisition of that asset by a member of the Group; and

(iii) the Security or Quasi-Security is removed or discharged within three months of the date of acquisition of such asset;

(f) any Security or Quasi-Security arising under any retention of title, hire purchase or conditional sale arrangement or arrangements having similar effect in respect of goods supplied to a member of the Group in the ordinary course of trading and on the supplier's standard or usual terms and not arising as a result of any default or omission by any member of the Group;

(g) any Quasi-Security arising as a result of a disposal which is a Permitted Disposal; or

(h) any Security or Quasi-Security arising as a consequence of any Finance Lease permitted pursuant to paragraph (f) of the definition of "Permitted Financial Indebtedness";

(i) any Security or Quasi-Security for taxes, assessments and other governmental charges or levies (excluding any Lien imposed pursuant to any of the provisions of ERISA) (i) not yet due or to which the period of grace, if any, related thereto has not expired of (ii) which are being contested in good faith, and by appropriate proceedings if adequate reserves are maintained to the extent required by GAAP;

(j) any Security or Quasi-Security relating to claims of materialmen, mechanics, carriers, warehousemen, processors or landlords for labour, materials, supplies or rentals incurred in the ordinary course of business, which (i) claims are being contested in good faith and by appropriate proceedings with adequate reserves

maintained to the extent required by GAAP and (ii) do not, individually or in the aggregate, materially impair the use thereof in the operation of the business of the Borrower or any of its Subsidiaries;

(k) deposits or pledges made in the ordinary course of business in connection with, or to secure payment of, obligations under workers' compensation, unemployment insurance and other types of social security or similar legislation, or to secure the performance of bids, trade contracts and leases (other than Financial Indebtedness), statutory obligations, surety bonds (other than bonds related to judgments or litigation), performance bonds and other obligations of a like nature incurred in the ordinary course of business;

(l) encumbrances in the nature of zoning restrictions, easements and rights or restrictions of record on the use of real property, which in the aggregate are not substantial in amount and which do not, in any case, materially impair the use thereof in the ordinary conduct of business;

(m) any Security or Quasi-Security arising from the filing of precautionary UCC financing statements relating solely to personal property leased pursuant to operating leases entered into in the ordinary course of business of the Borrower and its Subsidiaries;

(n) any Security or Quasi-Security securing judgments for the payment of money not constituting an Event of Default hereunder or securing appeal or other surety bonds relating to such judgments;

(o) any interest or title of a licensor, sub-licensor, lessor or sub-lessor with respect to any assets under any license or lease agreement entered into in the ordinary course of business which do not (i) interfere in any material respect with the business of the Borrower or its Subsidiaries or (ii) secure any Indebtedness; or

(p) Security or Quasi-Security not otherwise permitted hereunder securing Financial Indebtedness or other obligations in an aggregate principal amount not to exceed $5,000,000 at any time outstanding.

"**Permitted Share Issue**" means an issue of:

(a) shares by the Company, where such issue does not lead to a Change of Control of the Company; and

(b) shares by a member of the Group (other than the Company) which is a Subsidiary to its immediate Holding Company for non-cash consideration where (if the existing shares of the Subsidiary are the subject of the Transaction Security) the newly-issued shares also become subject to the Transaction Security on the same terms.

"**Permitted Transaction**" means:

(a) any disposal required, Financial Indebtedness incurred, guarantee, indemnity or Security or Quasi-Security given, or other transaction arising, under the Finance Documents;

(b) the solvent liquidation or reorganisation of any member of the Group which is not an Obligor or whose shares have not been charged or pledged under the Transaction Security Documents so long as any payments or assets distributed as a result of such liquidation or reorganisation are distributed to other members of the Group; or

(c) transactions (other than (i) any sale, lease, licence, transfer or other disposal; and (ii) the granting or creation of Security, the incurring or permitting to subsist of Financial Indebtedness or the disposal of the shares of any member of the Group), conducted in the ordinary course of trading on arm's length terms.

"**Plan**" means an employee pension benefit plan, as defined in Section 3(2) of ERISA (other than a Multiemployer Plan), subject to the provisions of Title IV of ERISA or Section 412 of the Code that is maintained or contributed to, or required to be contributed to, by any Obligor or ERISA Affiliate.

"**Product**" means any products, services, and diagnostic tests developed by the Group or any of its Subsidiaries or sold or marketed by any member of the Group or any of its Subsidiaries to third parties (and not for internal use by any member of the Group).

"**Property**" means any right or interest in or to property of any kind whatsoever, whether real, personal or mixed and whether tangible or intangible.

"**Qualified ECP Guarantor**" means, in respect of any Swap Obligation, each Obligor that has total assets exceeding $10,000,000 at the time such Swap Obligation is incurred or such other person as constitutes an “eligible contract participant” under the Commodity Exchange Act or any regulations promulgated thereunder and can cause another person to qualify as an “eligible contract participant” at such time by entering into a keepwell under Section 1a(18)(A)(v)(II) of the Commodity Exchange Act.

"**Qualifying Lender**" has the meaning given to that term in Clause 14 (*Tax Gross-Up and indemnities*).

"**Quarter Date**" means each of 31 March, 30 June, 30 September and 31 December.

"**Quarterly Financial Statements**" has the meaning given to that term in Clause 21 (*Information undertakings*).

"**Quasi-Security**" has the meaning given to that term in Clause 23.17 (*Negative pledge*).

"**Quotation Day**" means, in relation to any period for which an interest rate is to be determined:

(a) two US Government Securities Business Days before the first day of that period (unless market practice differs in the relevant syndicated loan market, in which case the Quotation Day will be determined by the Agent in accordance with that market practice (and if quotations would normally be given on more than one day, the Quotation Day will be the last of those days)); or

(b) if the Reference Rate is, or is based on, the Central Bank Rate, two US Government Securities Business Days before the first day of that period.

"**Receiver**" means a receiver or receiver and manager or administrative receiver of the whole or any part of the Charged Property.

"**Reference Rate**" means, in relation to any Loan:

(a) the applicable Term SOFR as of the Specified Time and for a period equal in length to the Interest Period of that Loan; or

(b) as otherwise determined pursuant to Clause 12.1 (*Unavailability of Term SOFR*),

and if, in either case, the aggregate of that rate and the Credit Adjustment Spread is less than one per cent. per annum, the Reference Rate shall be deemed to be such a rate that the aggregate of the Reference Rate and the Credit Adjustment Spread is one per cent. per annum.

"**Regulatory Agency**" means governmental authority or regulator with responsibility for the regulation of the research, development, marketing or sale of drugs or pharmaceuticals in any jurisdiction, including the FDA and the EMA.

"**Regulatory Approval**" means, with respect to a product or device in any country or regulatory jurisdiction, all actions, approvals (including, where applicable, pricing and reimbursement approval and schedule classifications), licenses, registrations or authorizations of any Regulatory Agency necessary for the making, manufacture, sale, offer for sale, distribution, import, export, promotion, marketing or other use of such product or device in such country or jurisdiction.

"**Related Fund**" means any (a) investment company, fund, trust, securitization vehicle or conduit that is (or will be) engaged in making, purchasing, holding or otherwise investing in commercial loans and similar extensions of credit in the ordinary course of business, or (b) any person (other than a natural person) which temporarily warehouses loans for any Lender or any entity described in the preceding clause (a) and that, with respect to each of the preceding clauses (a) and (b), is administered or managed by (i) a Lender, (ii) an Affiliate of a Lender or (iii) a person (other than a natural person) or an Affiliate of a person (other than a natural person) that administers or manages a Lender.

"**Relevant Jurisdiction**" means, in relation to an Obligor:

(a) its Original Jurisdiction;

(b) any jurisdiction where any asset subject to or intended to be subject to the Transaction Security to be created by it is situated;

(c) any jurisdiction where it conducts its business;

(d) the jurisdiction whose laws govern the perfection of any of the Transaction Security Documents entered into by it; and

(e) in the case of a US Obligor:

(i) the jurisdiction where it maintains its principal place of business; and

(ii) any jurisdiction the laws of which govern any Transaction Security Document or the attachment or perfection of any charge, lien, security interest or other encumbrance established or created pursuant thereto.

"**Relevant Market**" means the market for overnight cash borrowing collateralised by US Government securities.

"**Repayment Date**" means the first Business Day of each calendar Month.

"**Repayment Instalment**" means a Facility A Repayment Instalment as defined in Clause 6.1 (*Repayment of Facility A Loans*), a Facility B Repayment Instalment as defined in Clause 6.2 (*Repayment of the Facility B Loan*) or a Facility C Repayment Instalment as defined in Clause 6.3 (*Repayment of the Facility C Loan*).

"**Repeating Representations**" means each of the representations set out in Clause 20.2 (*Status*) to Clause 20.7 (*Governing law and enforcement*), Clause 20.11 (*No default*), Clause 20.20 (*Ranking*) to Clause 20.22 (*Legal and beneficial ownership*) and Clause 20.30 (*Sanctions*).

"**Report**" means any due diligence report prepared in connection with a Permitted Acquisition.

"**Reporting Day**" means:

(a) subject to paragraph (b) below, the Quotation Day for the relevant Interest Period; or

(b) if the Reference Rate is, or is based on, the Central Bank Rate, the date falling one Business Day after the Quotation Day for the relevant Interest Period.

"**Representative**" means any delegate, agent, manager, administrator, nominee, attorney, trustee or custodian.

"**Resignation Letter**" means a letter substantially in the form set out in Schedule 7 (*Form of Resignation Letter*).

"**Second Amendment and Restatement Agreement**" means the amendment and restatement agreement amending and restating this Agreement and made between, amongst others, the Company and the Agent dated _____ 2023.

"**Second Effective Date**" means the "Effective Date" under and as defined in the Second Amendment and Restatement Agreement.

"**Secured Parties**" means each Finance Party, any Receiver or Delegate.

"**Security**" means a mortgage, charge, pledge, lien or other security interest securing any obligation of any person or any other agreement or arrangement having a similar effect.

"**Security Agent's Spot Rate of Exchange**" means, in respect of the conversion of one currency (the "**First Currency**") into another currency (the "**Second Currency**") the Security Agent's spot rate of exchange for the purchase of the Second Currency with the First Currency in the London foreign exchange market at or about 11:00 am (London time) on a particular day, which shall be notified by the Security Agent in accordance with paragraph (e) of Clause 28.6 (*Duties of the Security Agent*).

"**Selection Notice**" means a notice substantially in the form set out in Part 2 of Schedule 3 (*Requests and Notices*) given in accordance with Clause 11 (*Interest Periods*) in relation to a Facility.

"**SOFR**" means the secured overnight financing rate (SOFR) administered by the Federal Reserve Bank of New York (or any other person which takes over the administration of that rate) published (before any correction, recalculation or republication by the administrator) by the Federal Reserve Bank of New York (or any other person which takes over the publication of that rate).

"**Specified Time**" means a time determined in accordance with Schedule 9 (*Timetables*).

"**Sterling**" and "**£**" means the lawful currency of the UK.

"**Subsidiary**" means an entity of which a person:

(a) has direct or indirect Control; or

(b) owns directly or indirectly more than fifty per cent. (50%) of the share capital or similar right of ownership; or

(c) is entitled to receive more than fifty per cent. (50%) of the dividends or distributions,

and any entity (whether or not so controlled) treated as a subsidiary in the latest financial statements of that person from time to time and disregarding, for the purpose of this definition, the fact that any shares in that entity may be held by way of security, that the beneficiary of the security (or its nominee) may be registered as a member of the relevant undertaking and/or that such beneficiary of the security (or its nominee) may be entitled to exercise voting powers and rights with respect to those charged shares.

"**Swap Obligation**" means, with respect to any Obligor or the Company, any obligation to pay or perform under any agreement, contract or transaction that constitutes a "swap" within the meaning of section 1a(47) of the Commodity Exchange Act.

"**Tax**" means any tax, levy, impost, duty or other charge or withholding of a similar nature (including any penalty or interest payable in connection with any failure to pay or any delay in paying any of the same).

"**Term SOFR**" means the term SOFR reference rate administered by CME Group Benchmark Administration Limited (or any other person which takes over the administration of that rate) for the relevant period published (before any correction, recalculation or republication by the administrator) by CME Group Benchmark Administration Limited (or any other person which takes over the publication of that rate).

"**Termination Date**" means in relation to each Facility, the date falling 60 months after the First Effective Date.

"**Total Commitments**" means the aggregate of the Total Facility A1 Commitments, Total Facility A2 Commitments, the Total Facility B Commitments and the Total Facility C Commitments, being $100,000,000 at the First Effective Date.

"**Total Facility A1 Commitments**" means the aggregate of the Facility A1 Commitments, being $25,000,000 at the First Effective Date.

"**Total Facility A2 Commitments**" means the aggregate of the Facility A2 Commitments, being $8,000,000 at the First Effective Date.

"**Total Facility B Commitments**" means the aggregate of the Facility B Commitments, being $33,000,000 at the First Effective Date.

"**Total Facility C Commitments**" means the aggregate of the Facility C Commitments, being $34,000,000 at the First Effective Date.

"**Trade Instruments**" means any performance bonds, advance payment bonds or documentary letters of credit issued in respect of the obligations of any member of the Group arising in the ordinary course of trading of that member of the Group.

"**Transaction Documents**" means the Finance Documents and the Constitutional Documents.

"**Transaction Security**" means the Security created or expressed to be created in favour of the Security Agent pursuant to the Transaction Security Documents.

"**Transaction Security Documents**" means each of the documents listed as being a Transaction Security Document in paragraph 13(a) of Part 1 of Schedule 2 (*Conditions precedent*), any document required to be delivered to the Agent under paragraph 13 of Part 2 of Schedule 2 (*Conditions precedent*) together with any other document entered into by any Obligor creating or expressed to create any Security over all or any part of its assets in respect of the obligations of any of the Obligors under any of the Finance Documents.

"**Transfer Certificate**" means a certificate substantially in the form set out in Schedule 4 (*Form of Transfer Certificate*) or any other form agreed between the Agent and the Company.

"**Transfer Date**" means, in relation to an assignment or transfer, the later of:

(a) the proposed Transfer Date specified in the relevant Assignment Agreement or Transfer Certificate; and

(b) the date on which the Agent executes the relevant Assignment Agreement or Transfer Certificate.

"**Treasury Transactions**" means any derivative transaction entered into in connection with protection against or benefit from fluctuation in any rate or price.

"**UCC**" means the Uniform Commercial Code as in effect from time to time in the State of New York; provided that if by reason of mandatory provisions of law, the perfection, the effect of perfection or non-perfection or the priority of the security interests in any collateral is governed by the Uniform Commercial Code as in effect in a jurisdiction other than New York, "UCC" means the Uniform Commercial Code as in effect in such other jurisdiction for purposes of the provisions hereof relating to such perfection, effect of perfection or non-perfection or priority.

"**UK**" and "**United Kingdom**" means the United Kingdom of Great Britain and Northern Ireland.

"**Unpaid Sum**" means any sum due and payable but unpaid by an Obligor under the Finance Documents.

"**US**" and "**United States**" means the United States of America.

"**US Bankruptcy Code**" means Title 11 of The United Stated Code (entitled "Bankruptcy"), as amended from time to time and as now or hereafter in effect, or any successor thereto.

"**US Debtor Relief Laws**" means the US Bankruptcy Code and all other federal and state liquidation, bankruptcy, assignment for the benefit of creditors, conservatorship, moratorium, receivership, insolvency, rearrangement, reorganization or similar debtor relief laws in effect from time to time.

"**US Government Securities Business Day**" means any day other than:

(a) a Saturday or a Sunday; and

(b) a day on which the Securities Industry and Financial Markets Association (or any successor organisation) recommends that the fixed income departments of its

members be closed for the entire day for purposes of trading in US Government securities.

"**US Guarantor**" means any Guarantor that is incorporated or organised under the laws of the United States or any State or territory thereof or the District of Columbia.

"**US Obligor**" means any Obligor that is incorporated or organised under the laws of the United States, any State or territory thereof or the District of Columbia.

"US Tax Obligor" means:

(a) a Borrower which is resident for tax purposes in the US; or

(b) an Obligor some or all of whose payments under the Finance Documents are from sources within the US for US federal income tax purposes.

"**Utilisation**" means a Loan.

"**Utilisation Date**" means the date of a Utilisation being the date on which the relevant Loan is to be made.

"**Utilisation Request**" means a notice substantially in the relevant form set out in Schedule 3 (*Requests*).

"**VAT**" means:

(a) any value added tax imposed by the Value Added Tax Act 1994;

(b) any tax imposed in compliance with the Council Directive of 28 November 2006 on the common system of value added tax (EC Directive 2006/112); and

(c) any other tax of a similar nature, whether imposed in the United Kingdom or in a member state of the European Union in substitution for, or levied in addition to, such tax referred to in paragraphs (a) or (b) above, or imposed elsewhere.

"**Withdrawal Liability**" means liability to a Multiemployer Plan as a result of a complete or partial withdrawal from such Multiemployer Plan, as such terms are defined in Part I of Subtitle E of Title IV of ERISA.

1.2 **Construction**

(a) Unless a contrary indication appears, a reference in this Agreement to:

(i) the "**Agent**", the "**Arranger**", any "**Finance Party**", any "**Lender**", any "**Obligor**", any "**Party**", any "**Secured Party**", the "**Security Agent**" or any other person shall be construed so as to include its successors in title, permitted assigns and permitted transferees to, or of, its rights and/or obligations under the Finance Documents and, in the case of the Security Agent, any person for the time being appointed as Security Agent or Security Agents in accordance with the Finance Documents;

(ii) a document in "**agreed form**" is a document which is previously agreed in writing by or on behalf of the Company and the Agent or, if not so agreed, is in the form specified by the Agent;

(iii) "**assets**" includes present and future properties, revenues and rights of every description;

(iv) a "**Finance Document**" or a "**Transaction Document**" or any other agreement or instrument is a reference to that Finance Document or Transaction Document or other agreement or instrument as amended, novated, supplemented or extended (in any case, however fundamentally);

(v) a "**group of Lenders**" includes all of the Lenders in that group;

(vi) "**guarantee**" means (other than in Clause 19 (*Guarantee and Indemnity*)) any guarantee, letter of credit, bond, indemnity or similar assurance against loss, or any obligation, direct or indirect, actual or contingent, to purchase or assume any indebtedness of any person or to make an investment in or loan to any person or to purchase assets of any person where, in each case, such obligation is assumed in order to maintain or assist the ability of such person to meet its indebtedness;

(vii) "**Guarantor**", "**Original Guarantor**", "**Additional Guarantor**" and "**this guarantee**" shall not be construed restrictively and shall include the payment undertakings and indemnities contained in Clause 19 (*Guarantee and Indemnity*);

(viii) "**including**" and "**in particular**" shall not be construed restrictively but shall mean "including without prejudice to the generality of the foregoing" and "in particular, but without limitation";

(ix) "**indebtedness**" includes any obligation (whether incurred as principal or as surety) for the payment or repayment of money, whether present or future, actual or contingent;

(x) a "**person**" includes any individual, firm, company, corporation, government, state or agency of a state or any association, joint venture, trust, consortium, partnership or other entity (whether or not having separate legal personality);

(xi) a "**regulation**" includes any regulation, rule, official directive, request, or guideline (whether or not having the force of law) of any governmental, intergovernmental or supranational body, agency or department of any regulatory, self-regulatory or other authority or organisation;

(xii) "**wholly owned subsidiary**" means a company or corporation that has no members except for:

(1) another company or corporation and that other company's or corporation's wholly-owned subsidiaries; or

(2) persons acting on behalf of that other company or corporation and that other company's or corporation's wholly-owned subsidiaries.

(xiii) a provision of law is a reference to that provision as amended or re-enacted and any subordinate legislation made under it;

(xiv) a time of day is a reference to London time;

(xv) a Lender's "**cost of funds**" in relation to its participation in a Loan is a reference to the average cost (determined either on an actual or a notional basis) which that Lender would incur if it were to fund, from whatever source(s) it may reasonably select, an amount equal to the amount of that participation in that Loan for a period equal in length to the Interest Period of that Loan; and

(xvi) the "**date of this Agreement**" means 24 May 2019.

(b) The determination of the extent to which a rate is "for a period equal in length" to an Interest Period shall disregard any inconsistency arising from the last day of that Interest Period being determined pursuant to the terms of this Agreement.

(c) Section, Clause and Schedule headings are for ease of reference only.

(d) Unless a contrary indication appears, a term used in any other Finance Document or in any notice given under or in connection with any Finance Document has the same meaning in that Finance Document or notice as in this Agreement.

(e) A Default or an Event of Default is "**continuing**" if it has not been remedied or waived.

(f) Any consent, waiver or approval required from a Finance Party under a Finance Document must be in writing and will be of no effect if not in writing.

(g) Reference to a monetary sum specified in the Base Currency in Clause 20 (*Representations*), Clause 21 (*Information undertakings*), Clause 22 (*Financial covenants*), Clause 23 (*General undertakings*) and/or Clause 24 (*Events of Default*) shall be deemed to include reference to the Base Currency Equivalent of such sum.

(h) A reference in this Agreement to a Central Bank Rate shall include any successor rate to, or replacement rate for, that rate.

1.3 **Third party rights**

(a) Unless expressly provided to the contrary in a Finance Document a person who is not a Party has no right under the Contracts (Rights of Third Parties) Act 1999 (the "**Third Parties Act**") to enforce or enjoy the benefit of any term of this Agreement.

(b) Notwithstanding any term of any Finance Document, the consent of any person who is not a Party is not required to rescind or vary this Agreement at any time.

SECTION 2

THE FACILITIES

2. **THE FACILITIES**

2.1 **The Facilities**

Subject to the terms of this Agreement, the Lenders make available to the Borrowers:

(a) a Base Currency term loan facility in an aggregate amount equal to the Total Facility A1 Commitments;

(b) a Base Currency term loan facility in an aggregate amount equal to the Total Facility A2 Commitments;

(c) a Base Currency term loan facility in an aggregate amount equal to the Total Facility B Commitments; and

(d) a Base Currency term loan facility in an aggregate amount equal to the Total Facility C Commitments.

2.2 **Increase**

(a) The Company may by giving prior notice to the Agent after the effective date of a cancellation of:

(i) the Available Commitments of a Defaulting Lender in accordance with Clause 7.5 (*Right of cancellation in relation to a Defaulting Lender*); or

(ii) the Commitments of a Lender in accordance with:

(1) Clause 7.1 (*Illegality*), or

(2) Paragraph (a) of Clause 7.4 (*Right of cancellation and repayment in relation to a single Lender*),

request that the Commitments relating to any Facility be increased (and the Commitments relating to that Facility shall be so increased) in an aggregate amount in the Base Currency of up to the amount of the Available Commitments or Commitments relating to that Facility so cancelled as follows:

(iii) the increased Commitments will be assumed by one or more Eligible Institutions (each an "**Increase Lender**") selected by the Company and each of which confirms in writing (whether in the relevant Increase Confirmation or otherwise) its willingness to assume and does assume all the obligations of a Lender corresponding to that part of the increased Commitments which it is to assume, as if it had been an Original Lender in respect of those Commitments;

(iv) each of the Obligors and any Increase Lender shall assume obligations towards one another and/or acquire rights against one another as the Obligors and the Increase Lender would have assumed and/or acquired had the Increase Lender been an Original Lender in respect of that part of the increased Commitments which it is to assume;

(v) each Increase Lender shall become a Party as a "Lender" and any Increase Lender and each of the other Finance Parties shall assume obligations towards one another and acquire rights against one another as that Increase Lender and those Finance Parties would have assumed and/or acquired had the Increase Lender been an Original Lender in respect of that part of the increased Commitments which it is to assume;

(vi) the Commitments of the other Lenders shall continue in full force and effect; and

(vii) any increase in the Commitments relating to a Facility shall, subject to the conditions set out in paragraphs (d) and (e) below, take effect on the date specified by the Company in the notice referred to above or any later date on which the Agent executes an otherwise duly completed Increase Confirmation delivered to it by the relevant Increase Lender.

(b) The Agent shall, subject to paragraph (c) below, as soon as reasonably practicable after receipt by it of a duly completed Increase Confirmation appearing on its face to comply with the terms of this Agreement and delivered in accordance with the terms of this Agreement, execute that Increase Confirmation.

(c) The Agent shall only be obliged to execute an Increase Confirmation delivered to it by an Increase Lender once it is satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations in relation to the assumption of the increased Commitments by that Increase Lender.

(d) Each Increase Lender, by executing the Increase Confirmation, confirms (for the avoidance of doubt) that the Agent has authority to execute on its behalf any amendment or waiver that has been approved by or on behalf of the requisite Lender or Lenders in accordance with this Agreement on or prior to the date on which the increase becomes effective in accordance with this Agreement and that it is bound by that decision to the same extent as it would have been had it been an Original Lender.

(e) The Company shall, on the date upon which the increase takes effect, pay to the Agent (for its own account) a fee of $3,500 and the Company shall promptly on demand pay the Agent and the Security Agent the amount of all costs and expenses (including legal fees) reasonably incurred by either of them and, in the case of the Security Agent, by any Receiver or Delegate in connection with any increase in Commitments under this Clause 2.2.

(f) The Company may pay to the Increase Lender a fee in the amount and at the times agreed between the Company and the Increase Lender in a Fee Letter.

(g) Neither the Agent nor any Lender shall have any obligation to find an Increase Lender and in no event shall any Lender whose Commitment is replaced by an Increase Lender be required to pay or surrender any of the fees received by such Lender pursuant to the Finance Documents.

(h) Clause 25.4 (*Limitation of responsibility of Existing Lenders*) shall apply mutatis mutandis in this Clause 2.2 in relation to an Increase Lender as if references in that Clause to:

(i) an "**Existing Lender**" were references to all the Lenders immediately prior to the relevant increase;

(ii) the "**New Lender**" were references to that "Increase Lender"; and

(iii) a "**re-transfer**" and "**re-assignment**" were references to respectively a "**transfer**" and "**assignment**".

2.3 **Finance Parties' rights and obligations**

(a) The obligations of each Finance Party under the Finance Documents are several. Failure by a Finance Party to perform its obligations under the Finance Documents does not affect the obligations of any other Party under the Finance Documents. No Finance Party is responsible for the obligations of any other Finance Party under the Finance Documents.

(b) The rights of each Finance Party under or in connection with the Finance Documents are separate and independent rights and any debt arising under the Finance Documents to a Finance Party from an Obligor is a separate and independent debt in respect of which a Finance Party shall be entitled to enforce its rights in accordance with paragraph (c) below. The rights of each Finance Party include any debt owing to that Finance Party under the Finance Documents and, for the avoidance of doubt, any part of a Loan or any other amount owed by an Obligor which relates to a Finance Party's participation in a Facility or its role under a Finance Document (including any such amount payable to the Agent on its behalf) is a debt owing to that Finance Party by that Obligor.

(c) A Finance Party may, except as specifically provided in the Finance Documents, separately enforce its rights under or in connection with the Finance Documents.

2.4 **Obligors' Agent**

(a) Each Obligor (other than the Company) by its execution of this Agreement or an Accession Deed irrevocably appoints the Company (acting through one or more authorised signatories) to act on its behalf as its agent in relation to the Finance Documents and irrevocably authorises:

(i) the Company on its behalf to supply all information concerning itself contemplated by the Finance Documents to the Finance Parties and to give all notices and instructions (including, in the case of a Borrower, Utilisation Requests), to make any agreements and to effect any amendments, supplements and variations capable of being given, made or effected by any Obligor notwithstanding that they may affect the Obligor, without further reference to or the consent of that Obligor; and

(ii) each Finance Party to give any notice, demand or other communication to that Obligor pursuant to the Finance Documents to the Company,

and in each case the Obligor shall be bound as though the Obligor itself had given the notices and instructions (including, without limitation, any Utilisation Requests) or executed or made the agreements or effected the amendments, supplements or variations, or received the relevant notice, demand or other communication.

(b) Every act, omission, agreement, undertaking, settlement, waiver, amendment, supplement, variation, notice or other communication given or made by the Obligors'

Agent or given to the Obligors' Agent under any Finance Document on behalf of another Obligor or in connection with any Finance Document (whether or not known to any other Obligor and whether occurring before or after such other Obligor became an Obligor under any Finance Document) shall be binding for all purposes on that Obligor as if that Obligor had expressly made, given or concurred with it. In the event of any conflict between any notices or other communications of the Obligors' Agent and any other Obligor, those of the Obligors' Agent shall prevail.

3. PURPOSE

3.1 Purpose

Each Borrower shall apply all amounts borrowed by it under a Facility towards the general corporate and working capital purposes of the Group.

3.2 Monitoring

No Finance Party is bound to monitor or verify the application of any amount borrowed pursuant to this Agreement.

4. CONDITIONS OF UTILISATION

4.1 Initial conditions precedent

(a) The Lenders will only be obliged to comply with Clause 5.4 (*Lenders' participation*) in relation to any Utilisation if on or before the Utilisation Date for that Utilisation, the Agent has received all of the documents and other evidence listed in Part 1 of Schedule 2 (*Conditions precedent*) in form and substance satisfactory to the Agent. The Agent shall notify the Company and the Lenders promptly upon being so satisfied.

(b) Other than to the extent that the Majority Lenders notify the Agent in writing to the contrary before the Agent gives the notification described in paragraph (a) above, the Lenders authorise (but do not require) the Agent to give that notification. The Agent shall not be liable for any damages, costs or losses whatsoever as a result of giving any such notification.

4.2 Further conditions precedent

Subject to Clause 4.1 (*Initial conditions precedent*), the Lenders will only be obliged to comply with Clause 5.4 (*Lenders' participation*) if:

(a) on the date of the Utilisation Request and on the proposed Utilisation Date:

(i) no Default is continuing or would result from the proposed Loan; and

(ii) the Repeating Representations to be made by each Obligor are true in all material respects;

(b) in the case of a Facility B Loan, no earlier than five Business Days before the proposed Utilisation Date, the Company has delivered to the Agent a certificate signed by two officers of the Company:

(i) confirming that either:

(1) **[***]**; or

(2) **[***]**; and

(ii) evidencing that the Group has at least $100,000,000 of Group Unrestricted Cash (the conditions in paragraph (b)(i) and (ii), above, collectively, the "**Facility B Utilisation Conditions**"); and

(c) in the case of a Facility C Loan, no earlier than five Business Days before the proposed Utilisation Date, the Company has delivered to the Agent a certificate signed by two officers of the Company:

(i) evidencing that Net Revenue for the twelve (12) month period ending on the month-end date for which a Compliance Certificate was most recently delivered (or required to be delivered pursuant to Clause 21.2), was at least $**[***]**; and

(ii) evidencing that the Group has at least $100,000,000 of Group Unrestricted Cash.

4.3 **Maximum number of Loans**

(a) The Borrower may not deliver a Utilisation Request if as a result of the proposed Utilisation:

(i) more than one Facility A1 Loan would be outstanding;

(ii) more than one Facility A2 Loan would be outstanding;

(iii) more than one Facility B Loan would be outstanding; or

(iv) more than one Facility C Loan would be outstanding.

(b) The Borrower may not request that a Facility A Loan, the Facility B Loan or the Facility C Loan be divided.

SECTION 3

UTILISATION

5. UTILISATION

5.1 Delivery of a Utilisation Request

A Borrower (or the Company of its behalf) may utilise a Facility by delivery to the Agent of a duly completed Utilisation Request not later than the Specified Time.

5.2 Completion of a Utilisation Request

(a) Each Utilisation Request is irrevocable and will not be regarded as having been duly completed unless:

(i) it identifies the Facility to be utilised;

(ii) the proposed Utilisation Date is a Business Day within the Availability Period applicable to that Facility;

(iii) the currency and amount of the Utilisation comply with Clause 5.3 (*Currency and amount*); and

(iv) the proposed Interest Period complies with Clause 11 (*Interest Periods*).

(b) Only one Utilisation may be requested in each Utilisation Request.

5.3 Currency and amount

(a) The currency specified in a Utilisation Request must be the Base Currency.

(b) The amount of the proposed Utilisation must be:

(i) an amount equal to the Available Facility for Facility A1;

(ii) an amount equal to the Available Facility for Facility A2;

(iii) an amount equal to the Available Facility for Facility B; or

(iv) an amount equal to the Available Facility for Facility C.

5.4 Lenders' participation

(a) If the conditions set out in this Agreement have been met, each Lender shall make its participation in each Loan available by the Utilisation Date through its Facility Office.

(b) The amount of each Lender's participation in each Loan will be equal to the proportion borne by its Available Commitment to the Available Facility immediately prior to making the Loan.

5.5 Cancellation of Commitment

(a) The Facility A1 Commitments which, at that time, are unutilised shall be immediately cancelled at the end of the Availability Period for Facility A1.

(b) The Facility A2 Commitments which, at that time, are unutilised shall be immediately cancelled at the end of the Availability Period for Facility A2.

(c) The Facility B Commitments which, at that time, are unutilised shall be immediately cancelled at the end of the Availability Period for Facility B.

(d) The Facility C Commitments which, at that time, are unutilised shall be immediately cancelled at the end of the Availability Period for Facility C.

SECTION 4

REPAYMENT, PREPAYMENT AND CANCELLATION

6. REPAYMENT

6.1 Repayment of Facility A Loans

(a) The Borrower under Facility A shall, commencing on the first Repayment Date following the date falling:

(i) if the Facility B Utilisation Conditions have not been satisfied as of such date, 18 Months after the First Effective Date; or

(ii) if the Borrower has delivered a certificate to Agent certifying that the Facility B Utilisation Conditions have been (and remain) satisfied as of such date, 30 Months after the First Effective Date; and

(iii) in each case, on each Repayment Date thereafter,

repay the Facility A Loans in instalments (each a "**Facility A Repayment Instalment**") by repaying on each such Repayment Date an amount equal to the aggregate amount of the Facility A Loans on either the date falling 18 Months pursuant to paragraph (i), or 30 Months pursuant to paragraph (ii) above (as applicable) after the First Effective Date is divided by the number of Repayment Dates remaining (including the Repayment Date on which the first payment is made) before the occurrence of the Termination Date, until such time as the Facility A Loans have been repaid in full.

(b) Notwithstanding paragraph (a) above, if the Borrower has delivered a certificate to Agent certifying that the Facility B Utilisation Conditions have been (and remain) satisfied as of such date at any time during the period commencing on the date that is 18 months after the First Effective Date and ending on 1 July 2023, the Borrower shall not be required to make any additional scheduled principal payments under Facility A on any Repayment Date occurring after the date on which the Utilisation of Facility B occurs until the date that is 30 months after the Original Effective Date and the Facility A Repayment Instalments for the remaining Repayment Dates will be recalculated accordingly.

6.2 Repayment of the Facility B Loan

(a) The Borrower under Facility B shall, commencing on the first Repayment Date following the date falling:

(i) 30 Months after the First Effective Date; and

(ii) in each case, on each Repayment Date thereafter,

repay the Facility B Loan in instalments (each a "**Facility B Repayment Instalment**") by repaying on each such Repayment Date an amount equal to the aggregate amount of the Facility B Loan divided by the number of Repayment Dates remaining (including the Repayment Date on which the first payment is made) before the occurrence of the Termination Date, until such time as the Facility B Loan has been repaid in full.

(b) The Borrower under Facility B shall, commencing on the first Repayment Date following the date falling 30 Months after the First Effective Date and, in each case, on each Repayment Date thereafter, repay the Loans in instalments (each a "**Facility B Repayment Instalment**") by repaying on each such Repayment Date an amount equal to the aggregate amount of the Facility B Loan divided by the number of Repayment Dates remaining (including the Repayment Date on which the first payment is made) before the occurrence of the Termination Date, until such time as the Facility B Loan has been repaid in full.

6.3 **Repayment of the Facility C Loan**

(a) The Borrower under Facility C shall, commencing on the first Repayment Date following the date falling:

(i) if the Facility B Utilisation Conditions have not been satisfied as of such date, 18 Months after the First Effective Date; or

(ii) if the Borrower has delivered a certificate to Agent certifying that the Facility B Utilisation Conditions have been (and remain) satisfied as of such date, 30 Months after the First Effective Date; and

repay the Facility C Loan in instalments (each a "**Facility C Repayment Instalment**") by repaying on each such Repayment Date an amount equal to the aggregate amount of the Facility C Loan on the date falling 18 Months or 30 Months, as applicable, after the First Effective Date divided by the number of Repayment Dates remaining (including the Repayment Date on which the first payment is made) before the occurrence of the Termination Date, until such time as the Facility C Loan has been repaid in full.

6.4 **Repayment of Loans**

(a) Notwithstanding the provisions of Clause 6.1 (*Repayment of Facility A Loans*), Clause 6.2 (*Repayment of the Facility B Loan*) and Clause 6.3 (*Repayment of the Facility C Loan*), the relevant Borrower of each Loan shall repay the outstanding principal amount of each Loan on the Termination Date.

(b) No Borrower may reborrow any part of a Facility which is repaid.

6.5 **Effect of cancellation and prepayment on scheduled repayments and reductions**

(a) If the Company cancels the whole or any Available Commitment in accordance with Clause 7.4 (*Right of cancellation and repayment in relation to a single Lender*) or Clause 7.5 (*Right of Cancellation in relation to a Defaulting Lender*) or if the Available Commitment of any Lender is cancelled under Clause 7.1 (*Illegality*) (other than, in any relevant case, to the extent that any part of relevant Available Commitment(s) so cancelled is subsequently increased pursuant to Clause 2.2 (*Increase*)); then the amount of the Repayment Instalment for each Repayment Date falling after that cancellation will reduce pro rata by the amount cancelled.

(b) If any Loan is repaid or prepaid in accordance with Clause 7.4 (*Right of cancellation and repayment in relation to a single Lender*) or Clause 7.1 (*Illegality*) then, other than to the extent that any part of the relevant Commitment is subsequently increased pursuant to Clause 2.2 (*Increase*) in the case of that Loan, the amount of the Repayment Instalments for the relevant Facility for each Repayment Date falling

after that repayment or prepayment will reduce *pro rata* by the amount of the Loan repaid or prepaid.

7. ILLEGALITY, VOLUNTARY PREPAYMENT AND CANCELLATION

7.1 Illegality

If in any applicable jurisdiction, it becomes unlawful for a Lender to perform any of its obligations as contemplated by this Agreement or to fund, issue or maintain its participation in any Utilisation or it becomes unlawful for any Affiliate of a Lender for that Lender to do so:

(a) that Lender shall promptly notify the Agent upon becoming aware of that event;

(b) upon the Agent notifying the Company, each Available Commitment of that Lender will be immediately cancelled; and

(c)

(i) each Borrower shall repay that Lender's participation in the Utilisations made to that Borrower on the last day of the Interest Period for each Utilisation occurring after the Agent has notified the Company or, if earlier, the date specified by the Lender in the notice delivered to the Agent (being no earlier than the last day of any applicable grace period permitted by law); and

(ii) that Lender's corresponding Commitment(s) shall be cancelled in the amount of the participations repaid.

7.2 Voluntary cancellation

The Company may, if it gives the Agent not less than 10 Business Days' (or such shorter period as the Majority Lenders may agree) prior notice, cancel the whole but not part of an Available Facility. Any cancellation under this Clause 7.2 shall reduce the Commitments of the Lenders rateably under that Facility.

7.3 Voluntary prepayment of Loans

(a) A Borrower to which a Loan has been made may, if it or the Company gives the Agent not less than 30 days' (or such shorter period as the Majority Lenders may agree) prior notice, prepay the whole but not part of that Loan.

(b) A Loan may only be prepaid after the last day of the Availability Period for the applicable Facility (or, if earlier, the day on which the applicable Available Facility is zero).

7.4 Right of cancellation and repayment in relation to a single Lender

(a) If:

(i) any sum payable to any Lender by an Obligor is required to be increased under paragraph (c) of Clause 14.2 (*Tax gross-up*); or

(ii) any Lender claims indemnification from the Company or an Obligor under Clause 14.3 (*Tax indemnity*) or Clause 15.1 (*Increased costs*),

the Company may, whilst the circumstance giving rise to the requirement for that increase or indemnification continues give the Agent notice of cancellation of the Commitment(s) of that Lender and its intention to procure the repayment of that Lender's participation in the Utilisations.

(b) On receipt of a notice referred to in paragraph (a) above in relation to a Lender, the Commitment(s) of that Lender shall immediately be reduced to zero.

(c) On the last day of each Interest Period which ends after the Company has given notice under paragraph (a)) above in relation to a Lender (or, if earlier, the date specified by the Company in that notice), each Borrower to which a Utilisation is outstanding shall repay that Lender's participation in that Utilisation together with all interest and other amounts accrued under the Finance Documents.

7.5 **Right of cancellation in relation to a Defaulting Lender**

(a) If any Lender becomes a Defaulting Lender, the Company may, at any time whilst the Lender continues to be a Defaulting Lender, give the Agent five Business Days' notice of cancellation of each Available Commitment of that Lender.

(b) On the notice referred to in paragraph (a) above becoming effective, each Available Commitment of the Defaulting Lender shall immediately be reduced to zero.

(c) The Agent shall as soon as practicable after receipt of a notice referred to in paragraph (a) above, notify all the Lenders.

8. **MANDATORY PREPAYMENT AND CANCELLATION**

8.1 **Exit**

(a) Upon the occurrence of:

(i) a Change of Control; or

(ii) the sale of all or substantially all of the assets of the Group whether in a single transaction or a series of related transactions,

the Facilities will be cancelled and all outstanding Utilisations, together with accrued interest, and all other amounts accrued under the Finance Documents, shall become immediately due and payable.

8.2 **Disposal, Insurance and Acquisition Proceeds**

(a) For the purposes of this Clause 8.2 and Clause 8.3 (*Application of mandatory prepayments and cancellations*):

"**Acquisition Proceeds**" means the proceeds of a claim or refund (a "**Recovery Claim**") against the vendor or any of its Affiliates (or any employee, officer or adviser) in relation to a Permitted Acquisition or against the provider of any Report (in its capacity as a provider of that Report) except for Excluded Acquisition Proceeds, and after deducting:

(i) any reasonable expenses which are incurred by any member of the Group to persons who are not members of the Group; and

(ii) any Tax incurred and required to be paid by a member of the Group (as reasonably determined by the relevant member of the Group on the basis of existing rates and taking into account any available credit, deduction or allowance),

in each case in relation to that Recovery Claim.

"**Disposal**" means a sale, lease, licence, transfer, loan or other disposal by a person of any asset, undertaking or business (whether by a voluntary or involuntary single transaction or series of transactions).

"**Disposal Proceeds**" means the consideration receivable by any member of the Group (including any amount receivable in repayment of intercompany debt) for any Disposal made by any member of the Group except for Excluded Disposal Proceeds and after deducting:

(i) any reasonable expenses which are incurred by any member of the Group with respect to that Disposal to persons who are not members of the Group; and

(ii) any Tax incurred and required to be paid by the seller in connection with that Disposal (as reasonably determined by the seller, on the basis of existing rates and taking account of any available credit, deduction or allowance).

"**Excluded Acquisition Proceeds**" means any proceeds of a Recovery Claim which the Company notifies the Agent are, or are to be, applied:

(i) in payment of amounts payable to the vendor in relation to a Permitted Acquisition by way of adjustment to the purchase price in respect of the relevant Permitted Acquisition (except to the extent relating to a working capital adjustment);

(ii) to satisfy (or reimburse a member of the Group which has discharged) any liability, charge or claim upon a member of the Group by a person which is not a member of the Group; or

(iii) in the replacement, reinstatement and/or repair of assets of members of the Group which have been lost, destroyed or damaged,

in each case as a result of the events or circumstances giving rise to that Recovery Claim, if those proceeds are so applied as soon as possible (but in any event within 180 days, or such longer period as the Majority Lenders may agree) after receipt.

"**Excluded Disposal Proceeds**" means

(i) Disposal Proceeds which have been derived from a Disposal of a type described in paragraphs (a), (b), (c), (d), (f) (but only if and to the extent that such Disposal is in exchange for other Cash Equivalent Investments), (g) or (h) of the definition of "Permitted Disposal"; and

(ii) any other Disposal Proceeds which are applied towards the purchase of replacement assets of the same general nature as those disposed of as soon as possible (but in any event within 180 days or such longer period as the Majority Lenders may agree) after receipt.

"**Excluded Insurance Proceeds**" means any proceeds of an insurance claim which the Company notifies the Agent are, or are to be, applied:

(i) to meet a third party claim; or

(ii) to cover operating losses in respect of which the relevant insurance claim was made; or

(iii) to the replacement, reinstatement and/or repair of the assets or otherwise in amelioration of the loss in respect of which the relevant insurance claim was made,

in each case as soon as possible (but in any event within 180 days, or such longer period as the Majority Lenders may agree) after receipt.

"**Insurance Proceeds**" means the proceeds of any insurance claim under any insurance maintained by any member of the Group except for Excluded Insurance Proceeds and after deducting any reasonable expenses in relation to that claim which are incurred by any member of the Group to persons who are not members of the Group.

(b) The Company shall ensure that the Borrowers prepay Utilisations and cancel Available Commitments, in amounts equal to the following amounts at the times and in the order of application contemplated by Clause 8.3 (*Application of mandatory prepayments and cancellations*):

(i) the amount of Acquisition Proceeds;

(ii) the amount of Disposal Proceeds; and

(iii) the amount of Insurance Proceeds.

8.3 **Application of mandatory prepayments and cancellations**

(a) A prepayment of Utilisations or cancellation of Available Commitments made under Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*) shall be applied in prepayment of Loans as contemplated in paragraphs (b) to (e) inclusive below.

(b) Unless the Company makes an election under paragraph (d) below, the Borrowers shall prepay Loans in the case of any prepayment relating to the amounts of Acquisition Proceeds, Disposal Proceeds or Insurance Proceeds, promptly upon receipt of those proceeds.

(c) A prepayment under Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*) shall prepay the Loans as follows:

(i) in amounts which reduce the Facility A Loans, the Facility B Loan and the Facility C Loan by the same proportion; and

(ii) in reducing the relevant Repayment Instalment for each Repayment Date falling after the date of prepayment in the manner contemplated by paragraph (d) of Clause 6.5 (*Effect of cancellation and prepayment on scheduled repayments and reductions*).

(d) Subject to paragraph (e) below, the Company may elect that any prepayment under Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*) be applied in

prepayment of a Loan on the last day of the Interest Period relating to that Loan. If the Company makes that election then a proportion of the Loan equal to the amount of the relevant prepayment will be due and payable on the last day of its Interest Period.

(e) If the Company has made an election under paragraph (d) above but a Default has occurred and is continuing, that election shall no longer apply and a proportion of the Loan in respect of which the election was made equal to the amount of the relevant prepayment shall be immediately due and payable (unless the Majority Lenders otherwise agree in writing).

8.4 **Excluded proceeds**

Where Excluded Acquisition Proceeds, Excluded Disposal Proceeds and Excluded Insurance Proceeds include amounts which are intended to be used for a specific purpose within a specified period (as set out in the relevant definition of Excluded Acquisition Proceeds, Excluded Disposal Proceeds or Excluded Insurance Proceeds), the Company shall ensure that those amounts are used for that purpose and shall promptly deliver a certificate to the Agent at the time of such application and at the end of such period confirming the amount (if any) which has been so applied within the requisite time periods provided for in the relevant definition.

9. RESTRICTIONS

9.1 **Notices of cancellation or prepayment**

Any notice of cancellation, prepayment, authorisation or other election given by any Party under Clause 7 (*Illegality, voluntary prepayment and cancellation*) or paragraph (d) of Clause 8.3 (*Application of mandatory prepayments and cancellations*) (subject to the terms of those Clauses) shall be irrevocable and, unless a contrary indication appears in this Agreement, shall specify the date or dates upon which the relevant cancellation or prepayment is to be made and the amount of that cancellation or prepayment.

9.2 **Interest and other amounts**

Any prepayment under this Agreement shall be made together with accrued interest on the amount prepaid and any prepayment fees that are payable under Clause 13.3 and, subject to any Break Costs, without premium or penalty.

9.3 **No reborrowing of Facilities**

No Borrower may reborrow any part of a Facility which is prepaid.

9.4 **Prepayment in accordance with Agreement**

No Borrower shall repay or prepay all or any part of the Utilisations or cancel all or any part of the Commitments except at the times and in the manner expressly provided for in this Agreement.

9.5 **No reinstatement of Commitments**

Subject to Clause 2.2 (*Increase*), no amount of the Total Commitments cancelled under this Agreement may be subsequently reinstated.

9.6 **Agent's receipt of notices**

If the Agent receives a notice under Clause 7 (*Illegality, voluntary prepayment and cancellation*), it shall promptly forward a copy of that notice to either the Company or the affected Lender, as appropriate.

9.7 **Effect of repayment and prepayment on Commitments**

If all or part of any Lender's participation in a Utilisation under a Facility is repaid or prepaid and is not available for redrawing (other than by operation of Clause 4.2 (*Further conditions precedent*)), an amount of that Lender's Commitment (equal to the amount in the Base Currency of the participation that is repaid or prepaid) in respect of that Facility will be deemed to be cancelled on the date of repayment or prepayment.

9.8 **Application of prepayments**

Any prepayment of a Utilisation (other than a prepayment pursuant to Clause 7.1 (*Illegality*) or Clause 7.4 (*Right of cancellation and repayment in relation to a single Lender*)) shall be applied *pro rata* to each Lender's participation in that Utilisation.

SECTION 5

COSTS OF UTILISATION

10. INTEREST

10.1 Calculation of interest

The rate of interest on each Loan for each Interest Period is the percentage rate per annum which is the aggregate of the applicable:

(a) Margin;

(b) Reference Rate; and

(c) Credit Adjustment Spread.

10.2 Payment of interest

The Borrower to which a Loan has been made shall pay accrued interest on that Loan on the last day of each Interest Period (and, if the Interest Period is longer than six Months, on the dates falling at six Monthly intervals after the first day of the Interest Period).

10.3 Default interest

(a) If an Obligor fails to pay any amount payable by it under a Finance Document on its due date, interest shall accrue on the overdue amount from the due date up to the date of actual payment (both before and after judgment) at a rate which, subject to paragraph (b) below, is 1 per cent per annum higher than the rate which would have been payable if the overdue amount had, during the period of non-payment, constituted a Loan in the currency of the overdue amount for successive Interest Periods, each of a duration selected by the Agent (acting reasonably). Any interest accruing under this Clause 10.3 shall be immediately payable by the Obligor on demand by the Agent.

(b) If any overdue amount consists of all or part of a Loan which became due on a day which was not the last day of an Interest Period relating to that Loan:

(i) the first Interest Period for that overdue amount shall have a duration equal to the unexpired portion of the current Interest Period relating to that Loan; and

(ii) the rate of interest applying to the overdue amount during that first Interest Period shall be 2 per cent per annum higher than the rate which would have applied if the overdue amount had not become due.

(c) Default interest (if unpaid) arising on an overdue amount will be compounded with the overdue amount at the end of each Interest Period applicable to that overdue amount but will remain immediately due and payable.

10.4 Notification of rates of interest

(a) The Agent shall promptly notify the relevant Lenders and the relevant Borrower (or the Company) of the determination of a rate of interest under this Agreement.

(b) The Agent shall promptly notify the relevant Borrower (or the Company) of each Funding Rate relating to a Loan.

10.5 **Maximum Rate of Interest**

In relation to the obligation of a US Obligor under this Agreement, notwithstanding anything to the contrary contained in any Finance Document, the interest paid or agreed to be paid under the Finance Documents shall not exceed the maximum rate of non-usurious interest permitted by applicable Law (the "**Maximum Rate**"). If a US Obligor is liable in relation to interest to be received by the Agent or any Lender in an amount that exceeds the Maximum Rate, the excess interest shall, in relation to any US Obligor only, be applied to the principal of the Loans or, if and as long as it exceeds such unpaid principal, the US Obligor shall not be liable under this Agreement and such amount shall be refunded to such US Obligor. In determining whether the interest contracted for, charged, or received by the Agent or a Lender exceeds the Maximum Rate, such person may, to the extent permitted by applicable law, (i) characterise any payment that is not principal as an expense, fee, or premium rather than interest, (ii) exclude voluntary prepayments and the effects thereof, and (iii) amortise, prorate, allocate, and spread in equal or unequal parts the total amount of interest throughout the contemplated term of the Loans and Letters of Credit hereunder.

11. **Interest Periods**

11.1 **Selection of Interest Periods and Terms**

(a) A Borrower (or the Company on behalf of a Borrower) may select an Interest Period for a Loan in the Utilisation Request for that Loan or (if the Loan has already been borrowed) in a Selection Notice.

(b) Each Selection Notice for a Loan is irrevocable and must be delivered to the Agent by the Borrower (or the Company on behalf of the Borrower) not later than the Specified Time.

(c) If a Borrower (or the Company) fails to deliver a Selection Notice to the Agent in accordance with paragraph (b) above, the relevant Interest Period will, subject to Clause 11.2 (*Changes to Interest Periods*), be one Month.

(d) Subject to this Clause 11, a Borrower (or the Company) may select an Interest Period of one Month or of any other period agreed between the Company, the Agent (and all the Lenders in relation to the relevant Loan). In addition a Borrower (or the Company on its behalf) may select an Interest Period of a period of less than one Month, if necessary to ensure that the Interest Period for the Loan ends on a Repayment Date relating to the relevant Facility for the Borrowers to make the Repayment Instalment due on that date.

(e) An Interest Period for a Loan shall not extend beyond the Termination Date.

(f) Each Interest Period for a Loan shall start on the relevant Utilisation Date or (if already made) on the last day of its preceding Interest Period.

11.2 **Changes to Interest Periods**

(a) Prior to determining the interest rate for any Loan, the Agent may shorten an Interest Period for that Loan to ensure the Interest Period for that Loan ends on the relevant Repayment Date for the Borrowers to make the relevant Repayment Instalment due on that date.

(b) If the Agent makes any of the changes to an Interest Period referred to in this Clause 11.2, it shall promptly notify the Company and the Lenders.

11.3 **Non-Business Days**

If an Interest Period would otherwise end on a day which is not a Business Day, that Interest Period will instead end on the next Business Day in that calendar month (if there is one) or the preceding Business Day (if there is not).

12. **CHANGES TO THE CALCULATION OF INTEREST**

12.1 **Unavailability of Term SOFR**

(a) *Interpolated Term SOFR*: If no Term SOFR is available for the Interest Period of a Loan, the applicable Reference Rate shall be the Interpolated Term SOFR for a period equal in length to the Interest Period of that Loan.

(b) *Fixed Central Bank Rate:* If no Term SOFR is available for the Interest Period of a Loan and it is not possible to calculate the Interpolated Term SOFR, the applicable Reference Rate shall be the percentage rate per annum which is the aggregate of:

(i) the Central Bank Rate for the Quotation Day; and

(ii) the applicable Central Bank Rate Adjustment.

(c) *Cost of funds*: If paragraph (b) above applies but there is no applicable Central Bank Rate, Clause 12.3 (*Cost of funds*) shall apply to that Loan for that Interest Period.

12.2 **Market disruption**

If before close of business in London on the Reporting Day the Agent receives notifications from a Lender or Lenders (whose participations in a Loan exceed 35 per cent. of that Loan) that its cost of funds relating to its participation in that Loan would be in excess of the Market Disruption Rate then Clause 12.3 (*Cost of funds*) shall apply to that Loan for the relevant Interest Period.

12.3 **Cost of funds**

(a) If this Clause 12.3 applies, the rate of interest on the relevant Loan for the relevant Interest Period shall be the percentage rate per annum which is the sum of:

(i) the Margin; and

(ii) the weighted average of the rates notified to the Agent by each Lender as soon as practicable and in any event by close of business on the date falling one Business Day after the Reporting Day (or, if earlier, on the date falling one Business Day before the date on which interest is due to be paid in respect of that Interest Period), to be that which expresses as a percentage rate per annum its cost of funds relating to its participation in that Loan.

(b) If this Clause 12.3 applies and the Agent or the Company so requires, the Agent and the Company shall enter into negotiations (for a period of not more than thirty days) with a view to agreeing a substitute basis for determining the rate of interest.

(c) Any alternative basis agreed pursuant to paragraph (b) above shall, with the prior consent of all the Lenders and the Company, be binding on all Parties.

(d) If this Clause 12.3 applies pursuant to Clause 12.2 (*Market disruption*) and:

(i) a Lender's Funding Rate is less than the Market Disruption Rate; or

(ii) a Lender does not notify a rate by the time specified in paragraph (a)(ii) above,

that Lender's cost of funds relating to its participation in that Loan for that Interest Period shall be deemed, for the purposes of paragraph (a) above, to be the Market Disruption Rate.

12.4 **Notification to Company**

If Clause 12.3 (*Cost of funds*) applies the Agent shall, as soon as is practicable, notify the Company.

12.5 **Break Costs**

(a) Each Borrower shall, within three Business Days of demand by a Finance Party, pay to that Finance Party its Break Costs attributable to all or any part of a Loan or Unpaid Sum being paid by that Borrower on a day prior to the last day of an Interest Period for that Loan or Unpaid Sum.

(b) Each Lender shall, as soon as reasonably practicable after a demand by the Agent, provide a certificate confirming the amount of its Break Costs for any Interest Period in respect of which they become, or may become, payable.

13. **Fees**

13.1 **Arrangement fee**

The Company shall pay to the Arranger an arrangement fee in the amount, manner and at the times agreed in a Fee Letter.

13.2 **Agency and Security Agent fee**

The Company shall pay to the Agent an agency fee in the amount, manner and at the times agreed in a Fee Letter.

13.3 **Prepayment fee**

If any Facility (or any part thereof) is prepaid or all or any part of the Commitments are cancelled for any reason, other than pursuant to Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*) (whether by voluntary prepayment by the Borrower, by reason of the occurrence of an Event of Default or the acceleration of any Facility, or otherwise, or if any Facility shall become accelerated and due and payable in full), in each case, prior to the third anniversary of the First Effective Date, the Borrower shall pay with the proposed prepayment a fee in an amount equal to:

(i) on or prior to the first anniversary of the First Effective Date, three per cent. of the amount of the principal repaid;

(ii) after the first anniversary but on or prior to the second anniversary of the First Effective Date, two per cent. of the amount of the principal repaid; and

(iii) after the second anniversary but on or prior to the third anniversary of the First Effective Date, one per cent. of the amount of the principal repaid.

13.4 **Final Payment fee**

The Company shall pay to the Agent a final payment fee in the amount, manner and at the times agreed in a Fee Letter.

SECTION 6

ADDITIONAL PAYMENT OBLIGATIONS

14. TAX GROSS UP AND INDEMNITIES

14.1 Definitions

In this Agreement:

"**Borrower DTTP Filing**" means an HM Revenue & Customs' Form DTTP2 duly completed and filed by the relevant Borrower, which:

(a) where it relates to a Treaty Lender that is an Original Lender, contains the scheme reference number and jurisdiction of tax residence stated opposite that Lender's name in Part 2 of Schedule 1 (*The Original Parties*), and:

(i) where the Borrower is an Original Borrower is filed with HM Revenue & Customs within 30 days of the Original Effective Date; or

(ii) where the Borrower is an Additional Borrower, is filed with HM Revenue & Customs within 30 days of the date on which that Borrower becomes an Additional Borrower, or

(b) where it relates to a Treaty Lender that is not an Original Lender, contains the scheme reference number and jurisdiction of tax residence stated in respect of that Lender in the documentation which it executes on becoming a Party as a Lender, and:

(i) where the Borrower is a Borrower as at the date on which that Treaty Lender becomes a Party as a Lender, is filed with HM Revenue & Customs within 30 days of that date; or

(ii) where the Borrower is not a Borrower as at the date on which that Treaty Lender becomes a Party as a Lender, is filed with HM Revenue & Customs within 30 days of the date on which that Borrower becomes an Additional Borrower;

"**Protected Party**" means a Finance Party which is or will be subject to any liability or required to make any payment for or on account of Tax in relation to a sum received or receivable (or any sum deemed for the purposes of Tax to be received or receivable) under a Finance Document;

"**Qualifying Lender**" means:

(a) a Lender which is beneficially entitled to interest payable to that Lender in respect of an advance under a Finance Document and is:

(i) a Lender:

(1) which is a bank (as defined for the purpose of section 879 of the ITA) making an advance under a Finance Document and is within the charge to United Kingdom corporation tax as respects any payments of interest made in respect of that advance or would be within such charge as respects such payments apart from section 18A of the CTA; or

(2) in respect of an advance made under a Finance Document by a person that was a bank (as defined for the purpose of section 879 of the ITA) at the time that that advance was made and within the charge to United Kingdom corporation tax as respects any payments of interest made in respect of that advance; or

(ii) a Lender which is:

(1) a company resident in the United Kingdom for United Kingdom tax purposes;

(2) a partnership each member of which is:

(aa) a company so resident in the United Kingdom; or

(bb) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account in computing its chargeable profits (within the meaning of section 19 of the CTA) the whole of any share of interest payable in respect of that advance that falls to it by reason of Part 17 of the CTA;

(3) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account interest payable in respect of that advance in computing the chargeable profits (within the meaning of section 19 of the CTA) of that company; or

(iii) a Treaty Lender; or

(b) a Lender which is a building society (as defined for the purposes of section 880 of the ITA) making an advance under a Finance Document;

"**Tax Confirmation**" means a confirmation by a Lender that the person beneficially entitled to interest payable to that Lender in respect of an advance under a Finance Document is either:

(a) a company resident in the United Kingdom for United Kingdom tax purposes;

(b) a partnership each member of which is:

(i) a company so resident in the United Kingdom; or

(ii) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account in computing its chargeable profits (within the meaning of section 19 of the CTA) the whole of any share of interest payable in respect of that advance that falls to it by reason of Part 17 of the CTA; or

(c) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account interest payable in respect of that advance in computing the chargeable profits (within the meaning of section 19 of the CTA) of that company;

"**Tax Credit**" means a credit against, relief or remission for, or repayment of, any Tax.

"**Tax Deduction**" means a deduction or withholding for or on account of Tax from a payment under a Finance Document, other than a FATCA Deduction.

"**Tax Payment**" means either the increase in a payment made by an Obligor to a Finance Party under Clause 14.2 (*Tax gross-up*) or a payment under Clause 14.3 (*Tax indemnity*).

"**Treaty Lender**" means a Lender which:

(a) is treated as a resident of a Treaty State for the purposes of the Treaty;

(b) does not carry on a business in the United Kingdom through a permanent establishment with which that Lender's participation in the Loan is effectively connected; and

(c) meets all other conditions in the Treaty for full exemption from Tax on interest imposed by the United Kingdom (except that for this purpose it shall be assumed that there is no special relationship between the Borrower and the Lender or between both of them and a third person), subject to completion of procedural formalities.

"**Treaty State**" means a jurisdiction having a double taxation agreement (a "**Treaty**") with the United Kingdom which makes provision for full exemption from tax imposed by the United Kingdom on interest;

"**UK Non-Bank Lender**" means:

(a) An Original Lender listed in Part 2 of Schedule 1 (*The Original Parties*); and

(b) a Lender which is not an Original Lender and which gives a Tax Confirmation in the documentation which it executes on becoming a Party as a Lender.

Unless a contrary indication appears, in this Clause 14.1 a reference to "**determines**" or "**determined**" means a determination made in the absolute discretion of the person making the determination.

14.2 **Tax gross-up**

(a) Each Obligor shall make all payments to be made by it under a Finance Document without any Tax Deduction, unless a Tax Deduction is required by law.

(b) The Company shall promptly upon becoming aware that an Obligor must make a Tax Deduction (or that there is any change in the rate or the basis of a Tax Deduction) notify the Agent accordingly. Similarly, a Lender shall promptly notify the Agent on becoming so aware in respect of a payment payable to that Lender. If the Agent receives such notification from a Lender it shall promptly notify the Company and that Obligor.

(c) If a Tax Deduction is required by law to be made by an Obligor, the amount of the payment due from that Obligor shall be increased to an amount which (after making any Tax Deduction) leaves an amount equal to the payment which would have been due if no Tax Deduction had been required.

(d) A payment shall not be increased under paragraph (c) above by reason of a Tax Deduction on account of Tax imposed by the United Kingdom, if on the date on which the payment falls due:

(i) the payment could have been made to the relevant Lender without a Tax Deduction if the Lender had been a Qualifying Lender, but on that date that Lender is not or has ceased to be a Qualifying Lender other than as a result of any change after the date it became a Lender under this Agreement in (or in the interpretation, administration, or application of) any law or Treaty, or any published practice or published concession of any relevant taxing authority; or

(ii) the relevant Lender is a Qualifying Lender solely by virtue of paragraph (a)(ii) of the definition of "Qualifying Lender"; and

(1) an officer of H.M. Revenue & Customs has given (and not revoked) a direction (a "**Direction**") under section 931 of the ITA which relates to the payment and that Lender has received from the Obligor making the payment or from the Company a certified copy of that Direction; and

(2) the payment could have been made to the Lender without any Tax Deduction if that Direction had not been made; or

(iii) the relevant Lender is a Qualifying Lender solely by virtue of paragraph (a)(ii) of the definition of "Qualifying Lender" and:

(1) the relevant Lender has not given a Tax Confirmation to the Company; and

(2) the payment could have been made to the Lender without any Tax Deduction if the Lender had given a Tax Confirmation to the Company, on the basis that the Tax Confirmation would have enabled the Company to have formed a reasonable belief that the payment was an "excepted payment" for the purpose of section 930 of the ITA; or

(iv) the relevant Lender is a Treaty Lender and the Obligor making the payment is able to demonstrate that the payment could have been made to the Lender without the Tax Deduction had that Lender complied with its obligations under paragraph (g) or (h) (as applicable) below.

(e) If an Obligor is required to make a Tax Deduction, that Obligor shall make that Tax Deduction and any payment required in connection with that Tax Deduction within the time allowed and in the minimum amount required by law.

(f) Within 30 days of making either a Tax Deduction or any payment required in connection with that Tax Deduction, the Obligor making that Tax Deduction shall deliver to the Agent for the Finance Party entitled to the payment a statement under section 975 of the ITA or other evidence reasonably satisfactory to that Finance Party that the Tax Deduction has been made or (as applicable) any appropriate payment paid to the relevant taxing authority.

(g)

(i) Subject to paragraph (ii) below, a Treaty Lender and each Obligor which makes a payment to which that Treaty Lender is entitled shall co-operate in completing any procedural formalities necessary for that Obligor to obtain authorisation to make that payment without a Tax Deduction (or with a reduced Tax Deduction);

(ii)

(1) a Treaty Lender which is an Original Lender and that holds a passport under the HMRC DT Treaty Passport scheme, and which wishes that scheme to apply to this Agreement, shall confirm its scheme reference number and its jurisdiction of tax residence opposite its name in Part 2 of Schedule 1 (*The Original Parties*); and

(2) a Treaty Lender which is not an Original Lender and that holds a passport under the HMRC DT Treaty Passport scheme, and which wishes that scheme to apply to this Agreement, shall confirm its scheme reference number and its jurisdiction of tax residence in the documentation which it executes on becoming a Party as a Lender,

and, having done so, that Lender shall be under no obligation pursuant to paragraph (i) above and the Borrower shall make a Borrower DTTP Filing.

(h) If a Lender has confirmed its scheme reference number and its jurisdiction of tax residence in accordance with paragraph (g)(ii) above and:

(i) a Borrower making a payment to that Lender has not made a Borrower DTTP Filing in respect of that Lender; or

(ii) a Borrower making a payment to that Lender has made a Borrower DTTP Filing in respect of that Lender but:

(1) that Borrower DTTP Filing has been rejected by HM Revenue & Customs; or

(2) HM Revenue & Customs has not given the Borrower authority to make payments to that Lender without a Tax Deduction within 60 days of the date of the Borrower DTTP Filing,

and in each case, the Borrower has notified that Lender in writing, that Lender and the Borrower shall co-operate in completing any additional procedural formalities necessary for that Borrower to obtain authorisation to make that payment without a Tax Deduction.

(i) If a Lender has not confirmed its scheme reference number and jurisdiction of tax residence in accordance with paragraph (g)(ii) above, no Obligor shall make a Borrower DTTP Filing or file any other form relating to the HMRC DT Treaty Passport scheme in respect of that Lender's Commitment(s) or its participation in any Utilisation unless the Lender otherwise agrees.

(j) A Borrower shall, promptly on making a Borrower DTTP Filing, deliver a copy of that Borrower DTTP Filing to the Agent for delivery to the relevant Lender.

(k) A UK Non-Bank Lender which is an Original Lender gives a Tax Confirmation to the Company by entering into this Agreement.

(l) A UK Non-Bank Lender shall promptly notify the Company and the Agent if there is any change in the position from that set out in the Tax Confirmation.

14.3 **Tax indemnity**

(a) The Company shall (within three Business Days of demand by the Agent) pay to a Protected Party an amount equal to the loss, liability or cost which that Protected Party determines will be or has been (directly or indirectly) suffered for or on account of Tax by that Protected Party in respect of a Finance Document.

(b) Paragraph (a) above shall not apply:

(i) with respect to any Tax assessed on a Finance Party:

(1) under the law of the jurisdiction in which that Finance Party is incorporated or, if different, the jurisdiction (or jurisdictions) in which that Finance Party is treated as resident for tax purposes; or

(2) under the law of the jurisdiction in which that Finance Party's Facility Office is located in respect of amounts received or receivable in that jurisdiction; or

(3) under the law of the jurisdiction in which the Finance Party otherwise has a permanent establishment (as defined in Article 5 of the OECD Model Tax Convention) through which it performs its obligations under the Finance Documents in respect of amounts received or receivable in that jurisdiction,

if that Tax is imposed on or calculated by reference to the net income received or receivable (but not any sum deemed to be received or receivable) by that Finance Party; or

(ii) to the extent a loss, liability or cost:

(1) is compensated for by an increased payment under Clause 14.2 (*Tax gross-up*), Clause 14.6 (*Stamp taxes*) or Clause 14.7 (*Value added tax*); or

(2) would have been compensated for by an increased payment under Clause 14.2 (*Tax gross-up*), Clause 14.6 (*Stamp taxes*) or Clause 14.7 (*Value added tax*) or Clause 15.1 (*Increased costs*) but was not so compensated solely because one of the exclusions in paragraph (d) of Clause 14.2 (*Tax gross-up*) , Clause 14.6 (*Stamp taxes*), Clause 14.7 (*Value added tax*) or Clause 15.3 (*Exceptions*) (other than paragraph (a)(iii) of Clause 15.3 (*Exceptions*)) (as applicable) applied; or

(3) is in respect of any Bank Levy (or any payment attributable to, or liability arising as a consequence of, a Bank Levy); or

(4) relates to a FATCA Deduction required to be made by a Party.

(c) A Protected Party making, or intending to make a claim under paragraph (a) above shall promptly notify the Agent of the event which will give, or has given, rise to the claim, following which the Agent shall notify the Company.

(d) A Protected Party shall, on receiving a payment from an Obligor under this Clause 14.3, notify the Agent.

14.4 **Tax Credit**

If an Obligor makes a Tax Payment and the relevant Finance Party determines that:

(a) a Tax Credit is attributable to an increased payment of which that Tax Payment forms part, to that Tax Payment or to a Tax Deduction in consequence of which that Tax Payment was required; and

(b) that Finance Party has obtained and utilised that Tax Credit,

the Finance Party shall pay an amount to the Obligor which that Finance Party determines will leave it (after that payment) in the same after-Tax position as it would have been in had the Tax Payment not been required to be made by the Obligor.

14.5 **Lender status confirmation**

Each Lender which is not an Original Lender shall indicate, in the documentation which it executes on becoming a Party as a Lender, and for the benefit of the Agent and without liability to any Obligor, which of the following categories it falls in:

(a) not a Qualifying Lender;

(b) a Qualifying Lender (other than a Treaty Lender); or

(c) a Treaty Lender.

If such a Lender fails to indicate its status in accordance with this Clause 14.5 then that Lender shall be treated for the purposes of this Agreement (including by each Obligor) as if it is not a Qualifying Lender until such time as it notifies the Agent which category applies (and the Agent upon receipt of such notification, shall inform the Company). For the avoidance of doubt, the documentation which a Lender executes on becoming a Party as a Lender shall not be invalidated by any failure of a Lender to comply with this Clause 14.5.

14.6 **Stamp taxes**

The Company shall pay and, within three Business Days of demand, indemnify each Finance Party against any cost, loss or liability that Finance Party incurs in relation to all stamp duty, registration and other similar Taxes payable in respect of any Finance Document, other than in connection with an assignment or transfer by a Lender of any rights under this Agreement.

14.7 **Value added tax**

(a) All amounts expressed to be payable under a Finance Document by any Party to a Finance Party which (in whole or in part) constitute the consideration for any supply for VAT purposes are deemed to be exclusive of any VAT which is chargeable on that supply, and accordingly, subject to paragraph (b) below, if VAT is or becomes chargeable on any supply made by any Finance Party to any Party under a Finance Document and such Finance Party is required to account to the relevant tax authority for the VAT, that Party must pay to such Finance Party (in addition to and at the same time as paying any other consideration for such supply) an amount

equal to the amount of the VAT (and such Finance Party must promptly provide an appropriate VAT invoice to that Party).

(b) If VAT is or becomes chargeable on any supply made by any Finance Party (the "**Supplier**") to any other Finance Party (the "**Recipient**") under a Finance Document, and any Party other than the Recipient (the "**Relevant Party**") is required by the terms of any Finance Document to pay an amount equal to the consideration for that supply to the Supplier (rather than being required to reimburse or indemnify the Recipient in respect of that consideration):

(i) (where the Supplier is the person required to account to the relevant tax authority for the VAT) the Relevant Party must also pay to the Supplier (at the same time as paying that amount) an additional amount equal to the amount of the VAT. The Recipient must (where this paragraph (i) applies) promptly pay to the Relevant Party an amount equal to any credit or repayment the Recipient receives from the relevant tax authority which the Recipient reasonably determines relates to the VAT chargeable on that supply; and

(ii) (where the Recipient is the person required to account to the relevant tax authority for the VAT) the Relevant Party must promptly, following demand from the Recipient, pay to the Recipient an amount equal to the VAT chargeable on that supply but only to the extent that the Recipient reasonably determines that it is not entitled to credit or repayment from the relevant tax authority in respect of that VAT.

(c) Where a Finance Document requires any Party to reimburse or indemnify a Finance Party for any cost or expense, that Party shall reimburse or indemnify (as the case may be) such Finance Party for the full amount of such cost or expense, including such part thereof as represents VAT, save to the extent that such Finance Party reasonably determines that it is entitled to credit or repayment in respect of such VAT from the relevant tax authority.

(d) Any reference in this Clause 14.7 to any Party shall, at any time when such Party is treated as a member of a group for VAT purposes, include (where appropriate and unless the context otherwise requires) a reference to the representative member of such group at such time (the term "representative member" to have the same meaning as in the Value Added Tax Act 1994).

(e) In relation to any supply made by a Finance Party to any Party under a Finance Document, if reasonably requested by such Finance Party, that Party must promptly provide such Finance Party with details of that Party's VAT registration and such other information as is reasonably requested in connection with such Finance Party's VAT reporting requirements in relation to such supply.

14.8 **FATCA Information**

(a) Subject to paragraph (c) below, each Party shall, within ten Business Days of a reasonable request by another Party:

(i) confirm to that other Party whether it is:

(1) a FATCA Exempt Party; or

(2) not a FATCA Exempt Party;

(ii) supply to that other Party such forms, documentation and other information relating to its status under FATCA as that other Party reasonably requests for the purposes of that other Party's compliance with FATCA;

(iii) supply to that other Party such forms, documentation and other information relating to its status as that other Party reasonably requests for the purposes of that other Party's compliance with any other law, regulation, or exchange of information regime.

(b) If a Party confirms to another Party pursuant to paragraph (a)(i) above that it is a FATCA Exempt Party and it subsequently becomes aware that it is not or has ceased to be a FATCA Exempt Party, that Party shall notify that other Party reasonably promptly.

(c) Paragraph (a) above shall not oblige any Finance Party to do anything, and paragraph (a)(iii) above shall not oblige any other Party to do anything, which would or might in its reasonable opinion constitute a breach of:

(i) any law or regulation;

(ii) any fiduciary duty; or

(iii) any duty of confidentiality.

(d) If a Party fails to confirm whether or not it is a FATCA Exempt Party or to supply forms, documentation or other information requested in accordance with paragraph (a)(i) or (a)(ii) above (including, for the avoidance of doubt, where paragraph (c) above applies), then such Party shall be treated for the purposes of the Finance Documents (and payments under them) as if it is not a FATCA Exempt Party until such time as the Party in question provides the requested confirmation, forms, documentation or other information.

(e) If a Borrower is a US Tax Obligor or if a Borrower or the Agent reasonably believes that its obligations under FATCA or any other applicable law or regulation require it, each Lender shall, within ten Business Days of:

(i) where an Original Borrower is a US Tax Obligor and the relevant Lender is an Original Lender, the Original Effective Date;

(ii) where a Borrower is a US Tax Obligor on a date on which any other Lender becomes a Party as a Lender, that date;

(iii) the date a new US Tax Obligor accedes as a Borrower; or

(iv) where a Borrower is not a US Tax Obligor, the date of a request from the relevant Borrower or the Agent,

supply to the Agent:

(1) a withholding certificate on Form W-8, Form W-9 or any other relevant form; or

(2) any withholding statement or other document, authorisation or waiver as the Agent may require to certify or establish the status of such Lender under FATCA or that other law or regulation.

(f) The Agent shall provide any withholding certificate, withholding statement, document, authorisation or waiver it receives from a Lender pursuant to paragraph (e) above to the relevant Borrower.

(g) If any withholding certificate, withholding statement, document, authorisation or waiver provided to the Agent by a Lender pursuant to paragraph (e) above is or becomes materially inaccurate or incomplete, that Lender shall promptly update it and provide such updated withholding certificate, withholding statement, document, authorisation or waiver to the Agent unless it is unlawful for the Lender to do so (in which case the Lender shall promptly notify the Agent). The Agent shall provide any such updated withholding certificate, withholding statement, document, authorisation or waiver to the relevant Borrower.

(h) The Agent may rely on any withholding certificate, withholding statement, document, authorisation or waiver it receives from a Lender pursuant to paragraph (e) or (g) above without further verification. The Agent shall not be liable for any action taken by it under or in connection with paragraphs (e), (f) or (g) above.

14.9 **FATCA Deduction**

(a) Each Party may make any FATCA Deduction it is required to make by FATCA, and any payment required in connection with that FATCA Deduction, and no Party shall be required to increase any payment in respect of which it makes such a FATCA Deduction or otherwise compensate the recipient of the payment for that FATCA Deduction.

(b) Each Party shall promptly, upon becoming aware that it must make a FATCA Deduction (or that there is any change in the rate or the basis of such FATCA Deduction), notify the Party to whom it is making the payment and, in addition, shall notify the Company and the Agent and the Agent shall notify the other Finance Parties.

15. **Increased Costs**

15.1 **Increased costs**

(a) Subject to Clause 15.3 (*Exceptions*) the Company shall, within three Business Days of a demand by the Agent, pay for the account of a Finance Party the amount of any Increased Costs incurred by that Finance Party or any of its Affiliates:

(i) as a result of (1) the introduction of or any change in (or in the interpretation, administration or application of) any law or regulation or (2) compliance with any law or regulation made after the Original Effective Date; or

(ii) attributable to the implementation or application of or compliance with Basel III or CRD IV or any other law or regulation which implements Basel III or CRD IV (whether such implementation, application or compliance is by a government, regulator, that Finance Party or any of its Affiliates) only to the extent not reasonably calculated prior to the Original Effective Date.

(b) In this Agreement:

(i) "**Increased Costs**" means:

(1) a reduction in the rate of return from a Facility or on a Finance Party's (or its Affiliate's) overall capital;

(2) an additional or increased cost; or

(3) a reduction of any amount due and payable under any Finance Document,

which is incurred or suffered by a Finance Party or any of its Affiliates but only to the extent attributable to that Finance Party having entered into its Commitment or funding or performing its obligations under any Finance Document.

(ii) "**Basel III**" means:

(1) the agreements on capital requirements, a leverage ratio and liquidity standards contained in "Basel III: A global regulatory framework for more resilient banks and banking systems", "Basel III: International framework for liquidity risk measurement, standards and monitoring" and "Guidance for national authorities operating the countercyclical capital buffer" published by the Basel Committee on Banking Supervision in December 2010, each as amended, supplemented or restated;

(2) the rules for global systemically important banks contained in "Global systemically important banks: assessment methodology and the additional loss absorbency requirement – Rules text" published by the Basel Committee on Banking Supervision in November 2011, as amended, supplemented or restated; and

(3) any further guidance or standards published by the Basel Committee on Banking Supervision relating to "Basel III;

(iii) "**CRD IV**" means:

(1) Regulation (EU) No 575/2013 of the European Parliament and of the Council of 26 June 2013 on prudential requirements for credit institutions and investment firms; and

(2) Directive 2013/36/EU of the European Parliament and of the Council of 26 June 2013 on access to the activity of credit institutions and the prudential supervision of credit institutions and investment firms, amending Directive 2002/87/EC and repealing Directives 2006/48/EC and 2006/49/EC;

or any law, rules or guidance by which either of them is implemented.

15.2 **Increased cost claims**

(a) A Finance Party intending to make a claim pursuant to Clause 15.1 (*Increased Costs*) shall notify the Agent of the event giving rise to the claim, following which the Agent shall promptly notify the Company.

(b) Each Finance Party shall, as soon as practicable after a demand by the Agent, provide a certificate confirming the amount of its Increased Costs.

15.3 **Exceptions**

(a) Clause 15.1 (*Increased costs*) does not apply to the extent any Increased Cost is:

(i) attributable to a Tax Deduction required by law to be made by an Obligor;

(ii) attributable to a FATCA Deduction required to be made by a Party;

(iii) compensated for by Clause 14.3 (*Tax indemnity*), Clause 14.6 (*Stamp taxes*) or Clause 14.7 (*Value added tax*) (or would have been compensated for under Clause 14.3 (*Tax indemnity*), Clause 14.6 (*Stamp taxes*) or Clause 14.7 (*Value added tax*) but was not so compensated solely because any of the exclusions in paragraph (b) of Clause 14.3 (*Tax indemnity*), Clause 14.6 (*Stamp taxes*) or Clause 14.7 (*Value added tax*) (as applicable) applied);

(iv) in respect of any Bank Levy (or any payment attributable to, or liability arising as a consequence of, a Bank Levy); or

(v) attributable to the wilful breach by the relevant Finance Party or its Affiliates of any law or regulation.

(b) In this Clause 15.3 reference to a "**Tax Deduction**" has the same meaning given to the term in Clause 14.1 (*Definitions*).

16. **OTHER INDEMNITIES**

16.1 **Currency indemnity**

(a) If any sum due from an Obligor under the Finance Documents (a "**Sum**"), or any order, judgment or award given or made in relation to a Sum, has to be converted from the currency (the "**First Currency**") in which that Sum is payable into another currency (the "**Second Currency**") for the purpose of:

(i) making or filing a claim or proof against that Obligor; or

(ii) obtaining or enforcing an order, judgment or award in relation to any litigation or arbitration proceedings,

that Obligor shall as an independent obligation, within three Business Days of demand, indemnify each Secured Party to whom that Sum is due against any cost, loss or liability arising out of or as a result of the conversion including any discrepancy between (1) the rate of exchange used to convert that Sum from the First Currency into the Second Currency and (2) the rate or rates of exchange available to that person at the time of its receipt of that Sum.

(b) Each Obligor waives any right it may have in any jurisdiction to pay any amount under the Finance Documents in a currency or currency unit other than that in which it is expressed to be payable.

16.2 **Other indemnities**

The Company shall (or shall procure that an Obligor will), within three Business Days of demand, indemnify the Arranger and each other Secured Party against any cost, loss or liability incurred by it as a result of:

(a) the occurrence or continuance of any Event of Default;

(b) a failure by an Obligor to pay any amount due under a Finance Document on its due date, including without limitation, any cost, loss or liability arising as a result of Clause 30 (*Sharing among the Finance Parties*);

(c) funding, or making arrangements to fund, its participation in a Utilisation requested by the Company or a Borrower in a Utilisation Request but not made by reason of the operation of any one or more of the provisions of this Agreement (other than by reason of default or negligence by that Finance Party alone);

(d) a Utilisation (or part of a Utilisation) not being prepaid in accordance with a notice of prepayment given by a Borrower or the Company.

16.3 **Indemnity to the Agent**

The Company shall promptly indemnify the Agent against:

(a) any cost, loss or liability incurred by the Agent (acting reasonably) as a result of:

(i) investigating any event which it reasonably believes is a Default;

(ii) acting or relying on any notice, request or instruction which it reasonably believes to be genuine, correct and appropriately authorised; or

(iii) instructing lawyers, accountants, tax advisers, surveyors or other professional advisers or experts as permitted under this Agreement; and

(b) any cost, loss or liability (including, without limitation, for negligence or any other category of liability whatsoever) incurred by the Agent (otherwise than by reason of the Agent's gross negligence or wilful misconduct) (or, in the case of any cost, loss or liability pursuant to Clause 31.11 (*Disruption to payment systems etc.*) notwithstanding the Agent's negligence, gross negligence or any other category of liability whatsoever but not including any claim based on the fraud of the Agent) in acting as Agent under the Finance Documents.

16.4 **Indemnity to the Security Agent**

(a) Each Obligor jointly and severally shall promptly indemnify the Security Agent and every Receiver and Delegate against any cost, loss or liability incurred by any of them as a result of:

(i) any failure by the Company to comply with its obligations under Clause 18 (*Costs and expenses*);

(ii) acting or relying on any notice, request or instruction which it reasonably believes to be genuine, correct and appropriately authorised;

(iii) the taking, holding, protection or enforcement of the Transaction Security;

(iv) the exercise of any of the rights, powers, discretions, authorities and remedies vested in the Security Agent and each Receiver and Delegate by the Finance Documents or by law;

(v) any default by any Obligor in the performance of any of the obligations expressed to be assumed by it in the Finance Documents; or

(vi) acting as Security Agent, Receiver or Delegate under the Finance Documents or which otherwise relates to any of the Charged Property (otherwise, in each case, than by reason of the relevant Security Agent's, Receiver's or Delegate's gross negligence or wilful misconduct).

(b) The Security Agent and every Receiver and Delegate may, in priority to any payment to the Secured Parties, indemnify itself out of the Charged Property in respect of, and pay and retain, all sums necessary to give effect to the indemnity in this Clause 16.4 and shall have a lien on the Transaction Security and the proceeds of the enforcement of the Transaction Security for all moneys payable to it.

17. MITIGATION BY THE LENDERS

17.1 Mitigation

(a) Each Finance Party shall, in consultation with the Company, take all reasonable steps to mitigate any circumstances which arise and which would result in any Facility ceasing to be available or any amount becoming payable under or pursuant to, or cancelled pursuant to, any of Clause 7.1 (*Illegality*), Clause 14 (*Tax gross-up and indemnities*) or Clause 15 (*Increased costs*) including (but not limited to) transferring its rights and obligations under the Finance Documents to another Affiliate or Facility Office.

(b) Paragraph (a) above does not in any way limit the obligations of any Obligor under the Finance Documents.

17.2 Limitation of liability

(a) The Company shall promptly indemnify each Finance Party for all costs and expenses reasonably incurred by that Finance Party as a result of steps taken by it under Clause 17.1 (*Mitigation*).

(b) A Finance Party is not obliged to take any steps under Clause 17.1 (*Mitigation*) if, in the opinion of that Finance Party (acting reasonably), to do so might be prejudicial to it.

18. COSTS AND EXPENSES

18.1 Transaction expenses

The Company shall promptly on demand pay the Agent, the Arranger and the Security Agent the amount of all costs and expenses (including pre-approved legal fees) reasonably incurred by any of them (and, in the case of the Security Agent, by any Receiver or Delegate) in connection with the negotiation, preparation, printing, execution, completion, syndication and perfection of:

(a) this Agreement and any other documents referred to in this Agreement and the Transaction Security; and

(b) any other Finance Documents executed after the Original Effective Date.

18.2 Amendment costs

If:

(a) an Obligor requests an amendment, waiver or consent; or

(b) an amendment is required pursuant to Clause 31.10 (*Change of currency*),

the Company shall, within three Business Days of demand, reimburse each of the Agent and the Security Agent for the amount of all costs and expenses (including legal fees) reasonably incurred by the Agent and the Security Agent (and, in the case of the Security Agent, by any Receiver or Delegate) in responding to, evaluating, negotiating or complying with that request or requirement.

18.3 **Security Agent's additional remuneration**

(a) In the event of:

(i) the occurrence of an Event of Default; or

(ii) the Security Agent and the Company agreeing that it is otherwise appropriate in the circumstances,

the Company shall pay to the Security Agent any additional remuneration that may be agreed between them or determined pursuant to paragraph (b) below.

(b) If the Security Agent and the Company fail to agree upon the nature of the duties, or upon the additional remuneration referred to in paragraph (a) above or whether additional remuneration is appropriate in the circumstances, any dispute shall be determined by an investment bank (acting as an expert and not as an arbitrator) selected by the Security Agent and approved by the Company or, failing approval, nominated (on the application of the Security Agent) by the President for the time being of the Law Society of England and Wales (the costs of the nomination and of the investment bank being payable by the Company) and the determination of any investment bank shall be final and binding upon the Parties.

18.4 **Enforcement and preservation costs**

The Company shall, within three Business Days of demand, pay to each Secured Party on a full indemnity basis the amount of all costs and expenses (including legal, valuation, accountancy and consulting fees and commission and out of pocket expenses) and any VAT thereon incurred by it in connection with the enforcement of or the preservation of or the release of any rights under any Finance Document or any of the documents referred to in such documents in any jurisdiction and any proceedings instituted by or against the Security Agent as a consequence of taking or holding the Transaction Security or enforcing these rights.

SECTION 7

GUARANTEE AND INDEMNITY

19. **GUARANTEE AND INDEMNITY**

19.1 **Guarantee and indemnity**

Each Guarantor irrevocably and unconditionally jointly and severally:

(a) guarantees to each Finance Party punctual performance by each other Obligor of all that Obligor's obligations under the Finance Documents (including, without limitation:

(i) obligations which, but for the automatic stay under section 362(a) of the US Bankruptcy Code, would become due; provided that, anything to the contrary contained in the foregoing notwithstanding, the obligations so guaranteed shall exclude any Excluded Swap Obligations; and

(ii) any interest accruing after the commencement of any proceeding under any US Debtor Relief Law at the rate provided for in this Agreement, whether or not such interest is an allowed claim in any such proceeding);

(b) undertakes with each Finance Party that whenever another Obligor does not pay any amount when due under or in connection with any Finance Document, that Guarantor shall immediately on demand pay that amount as if it was the principal obligor; and

(c) agrees with each Finance Party that if any obligation guaranteed by it is or becomes unenforceable, invalid or illegal, it will, as an independent and primary obligation, indemnify that Finance Party immediately on demand against any cost, loss or liability it incurs as a result of an Obligor not paying any amount which would, but for such unenforceability, invalidity or illegality have been payable by it under any Finance Document on the date when it would have been due. The amount payable by a Guarantor under this indemnity will not exceed the amount it would have had to pay under this Clause 19 if the amount claimed had been recoverable on the basis of a guarantee.

19.2 **Continuing guarantee**

This guarantee is a continuing guarantee and will extend to the ultimate balance of sums payable by any Obligor under the Finance Documents, regardless of any intermediate payment or discharge in whole or in part.

19.3 **Reinstatement**

If any discharge, release or arrangement (whether in respect of the obligations of any Obligor or any security for those obligations or otherwise) is made by a Finance Party in whole or in part on the basis of any payment, security or other disposition which is avoided or must be restored on insolvency, liquidation, administration or otherwise, without limitation, then the liability of each Guarantor under this Clause 19 will continue or be reinstated as if the discharge, release or arrangement had not occurred.

19.4 **Waiver of defences**

The obligations of each Guarantor under this Clause 19 will not be affected by an act, omission, matter or thing which, but for this Clause 19, would reduce, release or prejudice any of its obligations under this Clause 19 (without limitation and whether or not known to it or any Finance Party) including:

(a) any time, waiver or consent granted to, or composition with, any Obligor or other person;

(b) the release of any other Obligor or any other person under the terms of any composition or arrangement with any creditor of any member of the Group;

(c) the taking, variation, compromise, exchange, renewal or release of, or refusal or neglect to perfect, take up or enforce, any rights against, or security over assets of, any Obligor or other person or any non-presentation or non-observance of any formality or other requirement in respect of any instrument or any failure to realise the full value of any Security;

(d) any legal limitation, incapacity or lack of power, authority or legal personality of or dissolution or change in the members or status of an Obligor or any other person;

(e) any amendment, novation, supplement, extension or restatement (however fundamental and whether or not more onerous) or replacement of a Finance Document or any other document or Security including any change in the purpose of, any extension of or increase in any facility or the addition of any new facility under any Finance Document or other document or Security;

(f) any unenforceability, illegality, invalidity or frustration of any obligation of any person under any Finance Document or any other document or Security;

(g) the failure of any member of the Group to enter into or be bound by any Finance Document;

(h) any action (or decision not to act) taken by a Finance Party (or any trustee or agent on its behalf) in accordance with Clause 19.7 (*Appropriations*); or

(i) any insolvency, dissolution or similar proceedings or from any law, regulation or order.

Each Guarantor agrees that, as between that Guarantor and the Finance Parties, all amounts outstanding under this Agreement may be declared to be forthwith due and payable as provided in this Agreement for the purposes of this Clause 19, notwithstanding any stay (including under the US Bankruptcy Code), injunction or other prohibition preventing the same as against any other Obligor and that, in such event, all such amounts (whether or not due and payable by any such other Obligor) shall forthwith become due and payable by the Guarantor for the purposes of this Clause 19.

19.5 **Guarantor intent**

Without prejudice to the generality of Clause 19.4 (*Waiver of defences*), each Guarantor expressly confirms that it intends that this guarantee shall extend from time to time to any (however fundamental) variation, increase, extension or addition of or to any of the Finance Documents and/or any facility or amount made available under any of the Finance Documents for the purposes of or in connection with any of the following: acquisitions of

any nature; increasing working capital; enabling investor distributions to be made; carrying out restructurings; refinancing existing facilities; refinancing any other indebtedness; making facilities available to new borrowers; any other variation or extension of the purposes for which any such facility or amount might be made available from time to time; and any fees, costs and/or expenses associated with any of the foregoing.

19.6 **Immediate recourse**

Each Guarantor waives any right it may have of first requiring any Finance Party (or any trustee or agent on its behalf) to proceed against or enforce any other rights or security or claim payment from any person before claiming from that Guarantor under this Clause 19. This waiver applies irrespective of any law or any provision of a Finance Document to the contrary.

19.7 **Appropriations**

Until all amounts which may be or become payable by the Obligors under or in connection with the Finance Documents have been irrevocably paid in full, each Finance Party (or any trustee or agent on its behalf) may:

(a) refrain from applying or enforcing any other moneys, security or rights held or received by that Finance Party (or any trustee or agent on its behalf) in respect of those amounts, or apply and enforce the same in such manner and order as it sees fit (whether against those amounts or otherwise) and no Guarantor shall be entitled to the benefit of the same; and

(b) hold in an interest-bearing suspense account any moneys received from any Guarantor or on account of any Guarantor's liability under this Clause 19.

19.8 **Deferral of Guarantors' rights**

Until all amounts which may be or become payable by the Obligors under or in connection with the Finance Documents have been irrevocably paid in full and unless the Agent otherwise directs, no Guarantor will exercise any rights which it may have by reason of performance by it of its obligations under the Finance Documents or by reason of any amount being payable, or liability arising, under this Clause 19:

(a) to be indemnified by an Obligor;

(b) to claim any contribution from any other guarantor of any Obligor's obligations under the Finance Documents;

(c) to take the benefit (in whole or in part and whether by way of subrogation or otherwise) of any rights of the Finance Parties under the Finance Documents or of any other guarantee or security taken pursuant to, or in connection with, the Finance Documents by any Finance Party;

(d) to bring legal or other proceedings for an order requiring any Obligor to make any payment, or perform any obligation, in respect of which any Guarantor has given a guarantee, undertaking or indemnity under Clause 19.1 (*Guarantee and indemnity*);

(e) to exercise any right of set-off against any Obligor; and/or

(f) to claim or prove as a creditor of any Obligor in competition with any Finance Party;

If a Guarantor receives any benefit, payment or distribution in relation to such rights it shall hold that benefit, payment or distribution to the extent necessary to enable all amounts which may be or become payable to the Finance Parties by the Obligors under or in connection with the Finance Documents to be repaid in full on trust for the Finance Parties and shall promptly pay or transfer the same to the Agent or as the Agent may direct for application in accordance with Clause 31 (*Payment mechanics*).

19.9 **Contribution**

(a) At any time a payment is made pursuant to this Clause 19 (*Guarantee and Indemnity*) by a US Guarantor, the right of contribution of each US Guarantor against each other US Guarantor shall, subject to the other terms of this Clause 19, be determined as set out in paragraph (b) below with the right of contribution of each US Guarantor to be revised and restated each time a payment (a "**Relevant Payment"**) is made in relation to the obligations guaranteed under the Finance Documents provided, however, that no such right of contribution shall exist against any direct or indirect Non-US Subsidiary of such US Guarantor.

(b) If a Relevant Payment is made resulting in the aggregate payments made by such US Guarantor in respect of its guarantee obligations under the Finance Documents to and including the date of the Relevant Payment exceeding such US Guarantor's Contribution Percentage (as defined below) of the aggregate payments made by all US Guarantors in respect of the obligations under the Finance Documents to and including the date of the Relevant Payment (such excess, the "**Aggregate Excess Amount**"), each such US Guarantor shall have a right of contribution against each other US Guarantor (other than any direct or indirect Non-US Subsidiary of such US Guarantor) who has made payments in respect of the obligations under the Finance Documents to and including the date of the Relevant Payment in an aggregate amount less than such other US Guarantor's Contribution Percentage of the aggregate payments made to and including the date of the Relevant Payment by all US Guarantors in respect of the obligations under the Finance Documents (the aggregate amount of such deficit, the "**Aggregate Deficit Amount**") in an amount equal to:

(i) a fraction the numerator of which is the Aggregate Excess Amount of such US Guarantor and the denominator of which is the Aggregate Excess Amount of all US Guarantors,

multiplied by

(ii) the Aggregate Deficit Amount of such other US Guarantor (other than any direct or indirect Non-US Subsidiary of a US Guarantor).

(c) A US Guarantor's right of contribution under paragraph (b) above shall arise at the time of each computation, subject to adjustment to the time of each computation, provided that no US Guarantor may take any action to enforce such right until the obligations under the Finance Documents have been irrevocably paid in full in cash (or, in the case of contingent or unmatured obligations with respect to Letters of Credit, cash collateralized in a manner satisfactory to the Agent) and the Commitments hereunder (and thereunder) terminated or cancelled, it being expressly recognised and agreed by all Parties that any US Guarantor's right of contribution arising pursuant to this Clause 19 against any other US Guarantor shall be expressly junior and subordinate to such other US Guarantor's obligations and

liabilities in respect of the obligations under the Finance Documents and any other obligations owing under this Clause 19.

(d) As used in this Clause 19.9:

"**Adjusted Net Worth**" of each US Guarantor (other than any direct or indirect Non-US Subsidiary of a US Guarantor) shall mean the greater of (i) the Net Worth (as defined below) of such US Guarantor and (ii) zero;

"**Contribution Percentage**" of a US Guarantor shall mean the percentage obtained by dividing (i) the Adjusted Net Worth (as defined below) of such US Guarantor by (ii) the aggregate Adjusted Net Worth of all US Guarantors (other than any direct or indirect Non-US Subsidiary of a US Guarantor); and

"**Net Worth**" of each US Guarantor (other than any direct or indirect Non-US Subsidiary of a US Guarantor) shall mean the amount by which the fair saleable value of such US Guarantor's assets on the date of any Relevant Payment exceeds its existing debts and other liabilities (including contingent liabilities, but without giving effect to any obligations under the Finance Documents arising under this Clause 19 on such date.

(e) Notwithstanding anything to the contrary contained above, any US Guarantor that is released from this Clause 19 shall thereafter have no contribution obligations, or rights, pursuant to this Clause 19, and, at the time of any such release, if the released US Guarantor had an Aggregate Excess Amount or an Aggregate Deficit Amount, it shall be deemed reduced to US$0, and the contribution rights and obligations of the remaining US Guarantors shall be recalculated on the respective date of release (as otherwise provided above) based on the payments made hereunder by the remaining US Guarantors. All Parties recognise and agree that, except for any right of contribution arising pursuant to this Clause 19, each US Guarantor who makes any payment in respect of the obligations under the Finance Documents shall have no right of contribution or subrogation against any other US Guarantor in respect of such payment until all of the obligations under the Finance Documents have been irrevocably paid in full, in cash. Each of the US Guarantors recognises and acknowledges that the rights to contribution arising hereunder shall constitute an asset in favour of the party entitled to such contribution. In this connection, each US Guarantor has the right to waive its contribution right against any US Guarantor to the extent that giving effect to such waiver such US Guarantor would remain solvent, in the determination of the Majority Lenders. Notwithstanding anything to the contrary in this Clause 19, this Clause 19 will not be construed to limit the claim of any Finance Party under this Clause 19, the only such limitation being set forth in Clause 19.

19.10 **Release of Guarantors' right of contribution**

If any Guarantor (a "**Retiring Guarantor**") ceases to be a Guarantor in accordance with the terms of the Finance Documents for the purpose of any sale or other disposal of that Retiring Guarantor then on the date such Retiring Guarantor ceases to be a Guarantor:

(a) that Retiring Guarantor is released by each other Guarantor from any liability (whether past, present or future and whether actual or contingent) to make a contribution to any other Guarantor arising by reason of the performance by any other Guarantor of its obligations under the Finance Documents; and

(b) each other Guarantor waives any rights it may have by reason of the performance of its obligations under the Finance Documents to take the benefit (in whole or in part and whether by way of subrogation or otherwise) of any rights of the Finance Parties under any Finance Document or of any other security taken pursuant to, or in connection with, any Finance Document where such rights or security are granted by or relate to the assets of the Retiring Guarantor.

19.11 **Additional security**

This guarantee is in addition to and is not in any way prejudiced by any other guarantee or security now or subsequently held by any Finance Party.

19.12 **Guarantee limitations**

This guarantee does not apply to any liability to the extent that it would result in this guarantee constituting unlawful financial assistance within the meaning of sections 678 or 679 of the Companies Act 2006 or any equivalent and applicable provisions under the laws of the Original Jurisdiction of the relevant Guarantor and, with respect to any Additional Guarantor, is subject to any limitations set out in the Accession Deed applicable to such Additional Guarantor.

SECTION 8

REPRESENTATIONS, UNDERTAKINGS AND EVENTS OF DEFAULT

20. REPRESENTATIONS

20.1 General

(a) Each Obligor makes the representations and warranties set out in this Clause 20 to each Finance Party in accordance with Clause 20.34 (*Times when representations made*).

(b) For ease of reference only, the representations and warranties in Clause 20 marked with an asterisk are the Repeating Representations.

20.2 *Status

(a) It is a limited liability corporation, duly incorporated and validly existing under the law of its Original Jurisdiction.

(b) Each of its Subsidiaries is a limited liability corporation, or, in the case of any US Obligor or any such Subsidiary that is incorporated or organised in the United States or any State or territory thereof or the District of Columbia, a corporation or limited liability company, as applicable, duly incorporated and validly existing under the law of its jurisdiction of incorporation and for any US Obligor, (A) in good standing under the law of its jurisdiction of incorporation or organisation, as applicable, and (B) qualified to do business in each state or other jurisdiction where failure to be so qualified could reasonably be expected to have a Material Adverse Effect.

(c) It and each of its Subsidiaries has the power to own its assets and carry on its business as it is being conducted.

20.3 *Binding obligations

Subject to the Legal Reservations:

(a) the obligations expressed to be assumed by it in each Finance Document to which it is a party are legal, valid, binding and enforceable obligations; and

(b) (without limiting the generality of paragraph (a) above), each Transaction Security Document to which it is a party creates the security interests which that Transaction Security Document purports to create and those security interests are valid and effective.

20.4 *Non-conflict with other obligations

The entry into and performance by it of, and the transactions contemplated by, the Finance Documents and the granting of the Transaction Security do not and will not conflict with:

(a) any law or regulation applicable to it;

(b) the constitutional documents of any member of the Group; or

(c) any agreement or instrument binding upon it or any Obligor or any Obligor's assets or constitute a default or termination event (however described) under any such agreement or instrument.

20.5 ***Power and authority**

(a) It has the power to enter into, perform and deliver, and has taken all necessary action to authorise its entry into, performance and delivery of, the Finance Documents to which it is or will be a party and the transactions contemplated by those Finance Documents.

(b) No limit on its powers will be exceeded as a result of the borrowing, grant of security or giving of guarantees or indemnities contemplated by the Finance Documents to which it is a party.

20.6 ***Validity and admissibility in evidence**

(a) All Authorisations required or desirable:

(i) to enable it lawfully to enter into, exercise its rights and comply with its obligations in the Finance Documents to which it is a party; and

(ii) to make the Finance Documents to which it is a party admissible in evidence in its Relevant Jurisdictions,

have been obtained or effected and are in full force and effect except any Authorisation referred to in Clause 20.9 (*No filing or stamp taxes*), which Authorisations will be promptly obtained or effected after the Original Effective Date.

(b) All Authorisations necessary for the conduct of the business, trade and ordinary activities of members of the Group have been obtained or effected and are in full force and effect.

20.7 ***Governing law and enforcement**

(a) The law expressed to be the governing law in each Finance Document will be recognised and enforced in the Relevant Jurisdictions of each Obligor executing that Finance Document.

(b) Any judgment obtained in relation to a Finance Document in the jurisdiction of the governing law of that Finance Document will be recognised and enforced in its Relevant Jurisdictions.

20.8 **Insolvency**

No:

(a) corporate action, legal proceeding or other procedure or step described in paragraph (a) of Clause 24.7 (*Insolvency proceedings*); or

(b) creditors' process described in Clause 24.8 (*Creditors' process*),

has been taken or, to the knowledge of the Company, threatened in relation to a member of the Group; and none of the circumstances described in Clause 24.6 (*Insolvency*) applies to any member of the Group.

20.9 **No filing or stamp taxes**

Under the laws of its Relevant Jurisdiction it is not necessary that any Finance Document be filed, recorded or enrolled with any court or other authority in that jurisdiction or that any

stamp, registration, notarial or similar Taxes or fees be paid on or in relation to the Finance Documents or the transactions contemplated by the Finance Documents except:

(a) any filing, recording or enrolling or any tax or fee payable in relation to the Transaction Security Documents which are referred to in any Legal Opinion and which will be made or paid promptly after the date of the relevant Finance Document; and

(b) any stamp duty or similar Taxes chargeable in respect of a Transfer Certificate, Assignment Agreement or Increase Confirmation payable by a Finance Party.

20.10 **Deduction of Tax**

It is not required to make any Tax Deduction (as defined in Clause 14.1 (*Definitions*)) from any payment it may make under any Finance Document to a Lender which is:

(a) a Qualifying Lender:

(i) falling within paragraph (a)(i) of the definition of Qualifying Lender; or

(ii) except where a Direction has been given under section 931 of the ITA in relation to the payment concerned, falling within paragraph (a)(ii) of the definition of Qualifying Lender ; or

(iii) falling within paragraph (b) of the definition of Qualifying Lender or;

(b) a Treaty Lender and the payment is one specified in a direction given by the Commissioners of Revenue & Customs under Regulation 2 of the Double Taxation Relief (Taxes on Income) (General) Regulations 1970 (SI 1970/488).

20.11 ***No default**

(a) No Event of Default and, on the Original Effective Date and the Closing Date, no Default is continuing or is reasonably likely to result from the making of any Utilisation or the entry into, the performance of, or any transaction contemplated by, any Transaction Document.

(b) No other event or circumstance is outstanding which constitutes (or, with the expiry of a grace period, the giving of notice, the making of any determination or any combination of any of the foregoing would constitute) a default or termination event (however described) under any other agreement or instrument which is binding on it or any of its Subsidiaries or to which its (or any of its Subsidiaries') assets are subject which has or is reasonably likely to have a Material Adverse Effect.

20.12 **No misleading information**

Save as disclosed to the Agent in writing prior to the Original Effective Date:

(a) any factual information disclosed or contained in the Base Case Model was true and accurate in all material respects as at the date of the relevant report or document containing the information or (as the case may be) as at the date the information is expressed to be given;

(b) the Base Case Model has been prepared on a non-GAAP cash basis and is based on reasonable assumptions and have been approved by the board of directors of the Company;

(c) any financial projection or forecast contained in the Base Case Model has been prepared on a non-GAAP cash basis and on the basis of reasonable assumptions and was fair (as at the date of the relevant report or document containing the projection or forecast) and arrived at after careful consideration;

(d) the expressions of opinion or intention provided by or on behalf of an Obligor for the purposes of the Base Case Model were made after careful consideration and (as at the date of the relevant report or document containing the expression of opinion or intention) were fair and based on reasonable grounds; and

(e) no event or circumstance has occurred or arisen and no information has been omitted from the Base Case Model and no information has been given or withheld that results in the information, opinions, intentions, forecasts or projections contained in the Base Case Model being untrue or misleading in any material respect.

20.13 **Financial Statements**

(a) Its Original Financial Statements were prepared in accordance with the Accounting Principles consistently applied unless expressly disclosed to the Agent in writing to the contrary.

(b) Its Original Financial Statements fairly present its financial condition and its results of operations for the relevant period unless expressly disclosed to the Agent in writing to the contrary prior to the Original Effective Date.

(c) There has been no material adverse change in its assets, business or financial condition (or the assets, business or consolidated financial condition of the Group) in the case of the Company since the date of the Original Financial Statements.

(d) Its most recent financial statements delivered pursuant to Clause 21.1 (*Financial statements*):

(i) have been prepared in accordance with the Accounting Principles as applied to the Original Financial Statements; and

(ii) fairly present its consolidated financial condition as at the end of, and consolidated results of operations for, the period to which they relate.

(e) The budgets and forecasts supplied under this Agreement were arrived at after careful consideration and have been prepared in good faith on the basis of recent historical information and on the basis of assumptions which were reasonable as at the date they were prepared.

(f) Since the date of the most recent financial statements delivered pursuant to Clause 21.1 (*Financial statements*) there has been no material adverse change in the assets, business or financial condition of the Group.

20.14 **No proceedings**

(a) No litigation, arbitration or administrative proceedings or investigations of, or before, any court, arbitral body or agency which, if adversely determined, are reasonably likely to result in a judgment or liability of more than $5,000,000, that could have a Material Adverse Effect or that question the validity of the Finance Documents, have

(to the best of its knowledge and belief (having made due and careful enquiry)) been started or threatened against it or any of its Subsidiaries.

(b) No judgment or order of a court, arbitral body or agency which is reasonably likely to result in a judgment or liability of more than $5,000,000, that could have a Material Adverse Effect or that question the validity of the Finance Documents, has (to the best of its knowledge and belief (having made due and careful enquiry)) been made against it or any of its Subsidiaries.

20.15 **No breach of laws**

(a) It has not (and none of its Subsidiaries has) breached any law or regulation which breach has or is reasonably likely to have a Material Adverse Effect.

(b) No labour disputes are current or, to the best of its knowledge and belief (having made due and careful enquiry), threatened against any member of the Group which have or are reasonably likely to have a Material Adverse Effect.

20.16 **Environmental laws**

(a) Each member of the Group is in compliance with Clause 23.3 (*Environmental compliance*) and to the best of its knowledge and belief (having made due and careful enquiry) no circumstances have occurred which would prevent such compliance in a manner or to an extent which has or is reasonably likely to have a Material Adverse Effect.

(b) No Environmental Claim has been commenced or (to the best of its knowledge and belief (having made due and careful enquiry)) is threatened against any member of the Group where that claim has or is reasonably likely, if determined against that member of the Group, to have a Material Adverse Effect.

20.17 **Taxation**

(a) It is not (and none of its Subsidiaries is) overdue in the filing of any Tax returns and it is not (and none of its Subsidiaries is) overdue in the payment of any material amount in respect of Tax unless:

(i) such payment is being contested in good faith;

(ii) adequate reserves are being maintained for those Taxes and the costs required to contest them; and

(iii) such payment can be lawfully withheld and failure to pay those Taxes does not have or would not reasonably be expected to have a Material Adverse Effect.

(b) No claims or investigations are being or are reasonably likely to be made or conducted against it (or any of its Subsidiaries) with respect to Taxes such that a liability of, or claim against, any member of the Group which would have a Material Adverse Effect is reasonably likely to arise.

(c) It is resident for Tax purposes only in its Original Jurisdiction.

20.18 **Anti-corruption law**

Each member of the Group has conducted its businesses in compliance with applicable anti-corruption laws and has instituted and maintained policies and procedures designed to promote and achieve compliance with such laws.

20.19 **Security and Financial Indebtedness**

(a) No Security or Quasi-Security exists over all or any of the present or future assets of any member of the Group other than as permitted by this Agreement.

(b) No member of the Group has any Financial Indebtedness outstanding other than as permitted by this Agreement.

20.20 ***Ranking**

The Transaction Security has or will have first ranking priority and it is not subject to any prior ranking or pari passu ranking Security.

20.21 ***Good title to assets**

It and each of its Subsidiaries has a good, valid and marketable title to, or valid leases or licences of, and all appropriate Authorisations to use, the assets necessary to carry on its business as presently conducted.

20.22 ***Legal and beneficial ownership**

It and each of its Subsidiaries is the sole legal and beneficial owner of the respective assets over which it purports to grant Security to the Security Agent.

20.23 **Shares**

The shares of any member of the Group which are subject to the Transaction Security are fully paid and not subject to any option to purchase or similar rights. The constitutional documents of companies whose shares are subject to the Transaction Security do not and could not restrict or inhibit any transfer of those shares on creation or enforcement of the Transaction Security. There are no agreements in force which provide for the issue or allotment of, or grant any person the right to call for the issue or allotment of, any share or loan capital of any member of the Group (including any option or right of pre-emption or conversion).

20.24 **Intellectual Property**

It and each of its Subsidiaries:

(a) is the sole legal and beneficial owner of or has licensed to it on arm's length commercial terms all the Intellectual Property which is material in the context of its business and which is required by it in order to carry on its business as it is being conducted and as contemplated in the Base Case Model;

(b) does not (nor does any of its Subsidiaries), in carrying on its businesses, infringe any Intellectual Property of any third party in any respect which has or is reasonably likely to have a Material Adverse Effect; and

(c) has taken all formal or procedural actions (including payment of fees) required to maintain any material Intellectual Property owned by it.

20.25 **Group Structure Chart**

The Group Structure Chart is true, complete and accurate in all material respects.

20.26 **Accounting reference date**

The accounting reference date for each member of the Group is 31 December.

20.27 **Centre of main interests and establishments**

For the purposes of Regulation (EU) 2015/848 of 20 May 2015 on insolvency proceedings (recast) (the "**Regulation**"), its centre of main interest (as that term is used in Article 3(1) of the Regulation) is situated in its Original Jurisdiction and it has no "establishment" (as that term is used in Article 2(10) of the Regulation) in any other jurisdiction.

20.28 **Insurance**

There has been no non-disclosure, misrepresentation or breach of any term of any material insurance policy which would entitle any insurer to repudiate,, rescind or cancel it or to treat it as avoided in whole or in part or otherwise decline any valid claim under it by or on behalf of any member of the Group.

20.29 **Pensions**

Neither it nor any of its Subsidiaries is or has at any time been:

(a) an employer (for the purposes of Sections 38 to 51 of the Pensions Act 2004) of an occupational pension scheme which is not a money purchase scheme (both terms as defined in the Pensions Schemes Act 1993); and

(b) "connected" with or an "associate" of (as those terms are used in Sections 38 and 43 of the Pensions Act 2004) such an employer.

20.30 ***Sanctions**

Neither it nor any of its Subsidiaries, nor, to the knowledge of an Obligor, any directors, officers, employees, agents or affiliates of it or any of its Subsidiaries, is a person that, or is owned or controlled by a person that:

(a) listed, or is owned or controlled, directly or indirectly, by any person which is listed, on a Designated Parties List;

(b) located, organised or resident in a country which is the subject of sanctions by any Authority;

(c) a governmental agency, authority, or body or state-owned enterprise (or owned or controlled by any of the foregoing) of any country which is the subject of sanctions by any Authority; or

(d) a person or entity who is otherwise the target of sanctions by any Authority such that any Finance Party cannot deal or otherwise engage in business transactions with such person or entity.

20.31 **ERISA Plans**

(a) Except as would not be reasonably expected to have a Material Adverse Effect, each Plan complies in all respects with the applicable requirements of ERISA or the Code and all other applicable laws and regulations.

(b) Each Plan which is intended to be qualified under Section 401(a) of the Code has been determined by the IRS to be so qualified or is in the process of being submitted to the IRS for approval or will be so submitted during the applicable remedial amendment period, and, nothing has occurred since the date of such determination that would adversely affect such determination (or in the case of a Plan with no determination, nothing has occurred that would materially adversely affect such qualification).

(c) No ERISA Event has occurred or is reasonably likely to occur that has or would reasonably be expected to have a Material Adverse Effect.

(d) There is no litigation, arbitration, administrative proceeding or claim pending or to the knowledge of the Company threatened against or with respect to any Plan (other than routine claims for benefits) which could reasonably be expected to have a Material Adverse Effect.

(e) Except as would not be reasonably expected to have a Material Adverse Effect, no Obligor has any existing liability to the PBGC or any Plan and Multiemployer Plan (other than to make PBGC premium payments and Plan and Multiemployer Plan funding and contribution payments as they fall due).

(f) Each Obligor has made all contributions to each Plan and Multiemployer Plan as required by law within the applicable time limits prescribed by law, the terms of that Plan and any contract or agreement requiring contributions to the Plan except as could not reasonably be expected to have a Material Adverse Effect.

(g) No Obligor has ceased operations at a facility so as to become subject to the provisions of Section 4062(e) of ERISA, withdrawn as a substantial employer so as to become subject to the provisions of Section 4063 of ERISA, or ceased making contributions to any Plan subject to Section 4064(a) of ERISA to which it made contributions.

20.32 **Margin Stock**

No proceeds of any Utilisation will be used to purchase or carry any “margin stock” as defined in US Regulation U of the Board of Governors of the Federal Reserve System as in effect from time to time ("**Margin Stock**") or to extend credit for the purpose of purchasing or carrying any Margin Stock. Neither the making of any Utilisation nor the use of the proceeds of it will violate or be inconsistent with, or cause any Lender to violate, the provisions of US Regulation T, U or X of the Board of Governors of the Federal Reserve System in effect from time to time or any successor to all or a portion thereof. No member of the Group is engaged principally, or as one of its important activities, in the business whether immediate, incidental or ultimate, of buying or carrying Margin Stock or of extending

credit to others for the purpose, whether immediate, incidental or ultimate, of buying or carrying Margin Stock.

20.33 **Investment Company Act**

No US Obligor is or is required to be registered as an "investment company" within the meaning of the US Investment Company Act of 1940, as amended, or is otherwise subject to regulation under that Act.

20.34 **Times when representations made**

(a) All the representations and warranties in this Clause 20 are made by each Original Obligor on the Original Effective Date and the Closing Date.

(b) The Repeating Representations are deemed to be made by each Obligor:

(i) on the date of each Utilisation Request;

(ii) on each Utilisation Date; and

(iii) on the first day of each Interest Period.

(c) All the representations and warranties in this Clause 20 except Clause 20.12 (*No misleading information*) and Clause 20.25 (*Group Structure Chart*) and are deemed to be made by each Additional Obligor on the day on which it becomes (or it is proposed that it becomes) an Additional Obligor.

(d) Each representation or warranty deemed to be made after the Original Effective Date shall be deemed to be made by reference to the facts and circumstances existing at the date the representation or warranty is deemed to be made.

21. INFORMATION UNDERTAKINGS

The undertakings in this Clause 21 remain in force from the Original Effective Date for so long as any amount is outstanding under the Finance Documents or any Commitment is in force.

In this Clause 21:

"**Annual Financial Statements**" means the financial statements for a Financial Year delivered pursuant to paragraph (a) of Clause 21.1 (*Financial statements*).

"**Quarterly Financial Statements**" means the financial statements delivered pursuant to paragraph (b) of Clause 21.1 (*Financial statements*).

21.1 **Financial statements**

The Company shall supply to the Agent in sufficient copies for all the Lenders:

(a) as soon as they are available, but in any event within 90 days after the end of each of its Financial Years:

(i) its audited consolidated financial statements for that Financial Year;

(ii) the audited financial statements (consolidated if appropriate) of each Obligor for that Financial Year; and

(iii) the audited financial statements of any other member of the Group for that Financial Year if requested by the Agent; and

(b) as soon as they are available, but in any event within 45 days after the end of each Financial Quarter of each of its Financial Years its consolidated financial statements for that Financial Quarter.

21.2 **Provision and contents of Compliance Certificate**

(a) The Company shall supply a Compliance Certificate to the Agent with each set of its Annual Financial Statements, each set of its Quarterly Financial Statements and within 30 days after the end of each month.

(b) The Compliance Certificate shall include evidence as to (i) compliance with Clause 22 (*Financial covenants*) and (ii) the aggregate amount of cash and cash equivalents held by the Group and the aggregate amount of Group Unrestricted Cash as of the date of such Compliance Certificate.

(c) Each Compliance Certificate shall be signed by any two directors or officers (including the general counsel), one of whom must be the Chief Financial Officer of the Group.

21.3 **Requirements as to financial statements**

(a) The Company shall procure that

(i) each set of Annual Financial Statements and Quarterly Financial Statements includes a balance sheet, profit and loss account and cash flow statement; and

(ii) each set of its Annual Financial Statements shall be audited by the Company's Auditors.

(b) Each set of financial statements delivered pursuant to Clause 21.1 (*Financial statements*):

(i) shall be certified by the Chief Financial Officer as fairly presenting, its financial condition and operations as at the date as at which those financial statements were drawn up;

(ii) in the case of consolidated financial statements of the Group, shall be accompanied by a statement by the Chief Financial Officer comparing actual performance for the period to which the financial statements relate to:

(1) the projected performance for that period set out in the Budget; and

(2) the actual performance for the corresponding period in the preceding Financial Year of the Group; and

(3) shall be prepared using the Accounting Principles consistently applied.

21.4 **Budget**

(a) The Company shall supply to the Agent in sufficient copies for all the Lenders, as soon as the same become available but in any event within 60 days after the start

of each of its Financial Years, an annual Budget for that Financial Year as approved by the board of directors of the Company.

(b) If the Company updates or changes the Budget, it shall as soon as reasonably practicable deliver to the Agent, in sufficient copies for each of the Lenders, such updated or changed Budget together with a written explanation of the main changes in that Budget.

21.5 **Year-end**

The Company shall procure that the end of each annual accounting period of each member of the Group falls on the same date.

21.6 **Information: miscellaneous**

The Company shall supply to the Agent (in sufficient copies for all the Lenders, if the Agent so requests):

(a) at the same time as they are dispatched, copies of all documents dispatched by the Company to its shareholders generally (or any class of them) or dispatched by the Company or any Obligors to its creditors generally (or any class of them);

(b) upon becoming aware of them, the details of any litigation, arbitration or administrative proceedings which are current, threatened or pending against any member of the Group, and which, if adversely determined are reasonably likely to have a Material Adverse Effect;

(c) upon becoming aware of the relevant claim the details of any claim which is current, threatened or pending against the provider of a Report in respect of a Permitted Acquisition and details of any disposal or insurance claim which will require a prepayment under Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*);

(d) promptly, such information as the Security Agent may reasonably require about the Charged Property and compliance of the Obligors with the terms of any Transaction Security Documents; and

(e) promptly on request, such further information regarding the financial condition, assets and operations of the Group and/or any member of the Group as any Finance Party through the Agent may reasonably request.

21.7 **Notification of default**

(a) Each Obligor shall notify the Agent of any Default (and the steps, if any, being taken to remedy it) promptly upon becoming aware of its occurrence (unless that Obligor is aware that a notification has already been provided by another Obligor).

(b) Promptly upon a request by the Agent, the Company shall supply to the Agent a certificate signed by two of its senior officers on its behalf certifying that no Default is continuing (or if a Default is continuing, specifying the Default and the steps, if any, being taken to remedy it).

21.8 **"Know your customer" checks**

(a) If:

(i) the introduction of or any change in (or in the interpretation, administration or application of) any law or regulation made after the Original Effective Date;

(ii) any change in the status of an Obligor (or of a Holding Company of an Obligor) or the composition of the shareholders of an Obligor (or of a Holding Company of an Obligor) after the Original Effective Date; or

(iii) a proposed assignment or transfer by a Lender of any of its rights and/or obligations under this Agreement to a party that is not a Lender prior to such assignment or transfer,

obliges the Agent or any Lender (or, in the case of paragraph (iii) above, any prospective new Lender) to comply with "know your customer" or similar identification procedures in circumstances where the necessary information is not already available to it, each Obligor shall promptly upon the request of the Agent or any Lender supply, or procure the supply of, such documentation and other evidence as is reasonably requested by the Agent (for itself or on behalf of any Lender) or any Lender (for itself or, in the case of the event described in paragraph (iii) above, on behalf of any prospective new Lender) in order for the Agent, such Lender or, in the case of the event described in paragraph (iii) above, any prospective new Lender to carry out and be satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations pursuant to the transactions contemplated in the Finance Documents.

(b) Each Lender shall promptly upon the request of the Agent supply, or procure the supply of, such documentation and other evidence as is reasonably requested by the Agent (for itself) in order for the Agent to carry out and be satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations pursuant to the transactions contemplated in the Finance Documents.

(c) The Company shall, by not less than 10 Business Days' prior written notice to the Agent, notify the Agent (which shall promptly notify the Lenders) of its intention to request that one of its Subsidiaries becomes an Additional Obligor pursuant to Clause 26 (*Changes to the Obligors*).

(d) Following the giving of any notice pursuant to paragraph (c) above, if the accession of such Additional Obligor obliges the Agent or any Lender to comply with "know your customer" or similar identification procedures in circumstances where the necessary information is not already available to it, the Company shall promptly upon the request of the Agent or any Lender supply, or procure the supply of, such documentation and other evidence as is reasonably requested by the Agent (for itself or on behalf of any Lender) or any Lender (for itself or on behalf of any prospective new Lender) in order for the Agent, or such Lender or any prospective new Lender to carry out and be satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations pursuant to the accession of such Subsidiary to this Agreement as an Additional Obligor.

(e) Without limiting the generality of the foregoing, each Lender and the Agent (for itself and not on behalf of any Lender) hereby notifies each Obligor that pursuant to the requirements of the USA PATRIOT Act (Title III of Pub Law 107 56 (signed into law 26 October 2001)) (as amended from time to time, the "**Patriot Act**"), it is required to obtain, verify and record information that identifies each Obligor, which information includes the name of each Obligor and other information that will allow such Lender to identify each Obligor in accordance with the PATRIOT Act, and each Obligor hereby agrees to provide such information from time to time to such Lender and the Agent, as applicable.

22. FINANCIAL COVENANTS

22.1 **Financial condition**

The Company shall ensure that:

(a) following the first Utilisation of Facility B, the Group Unrestricted Cash held by the Group shall not at any time be less than $20,000,000; and

(b) following the first Utilisation of Facility C, the Group Unrestricted Cash held by the Group shall not at any time be less than $35,000,000.

22.2 **Financial testing**

(a) Subject to paragraph (b) below, the financial covenants set out in Clause 22.1 (*Financial condition*) shall be calculated in accordance with the Accounting Principles and tested by reference to each of the financial statements delivered pursuant to paragraphs (a) and (b) of Clause 21.1 (*Financial statements*) and/or each Compliance Certificate delivered pursuant to Clause 21.2 (*Provision and contents of Compliance Certificate*).

(b) When calculating the financial covenants in this Clause the effect of all transactions between members of the Group shall be eliminated to the extent not already netted out on consolidation.

(c) No item shall be deducted or credited more than once in any calculation.

(d) Where an amount in any financial statement or Compliance Certificate is not denominated in the Base Currency, it shall be converted into the Base Currency at the rate specified in the financial statements so long as such rate has been set in accordance with the Accounting Principles.

(e) The financial covenants in paragraphs (a) and (b) of Clause 22.1 (*Financial condition*) shall apply on a continuing basis.

23. GENERAL UNDERTAKINGS

The undertakings in this Clause 23 remain in force from the Original Effective Date for so long as any amount is outstanding under the Finance Documents or any Commitment is in force.

Authorisations and compliance with laws

23.1 **Authorisations**

Each Obligor shall promptly:

(a) obtain, comply with and do all that is necessary to maintain in full force and effect; and

(b) supply certified copies to the Agent of,

any Authorisation required under any law or regulation of a Relevant Jurisdiction to:

(i) enable it to perform its obligations under the Finance Documents;

(ii) ensure the legality, validity, enforceability or admissibility in evidence of any Finance Document; and

(iii) carry on its business where failure to do so has or is reasonably likely to have a Material Adverse Effect.

23.2 **Compliance with laws**

Each Obligor shall (and the Company shall ensure that each member of the Group will) comply in all respects with all laws to which it may be subject, if failure so to comply has or is reasonably likely to have a Material Adverse Effect.

23.3 **Environmental compliance**

Each Obligor shall (and the Company shall ensure that each member of the Group will):

(a) comply with all Environmental Law;

(b) obtain, maintain and ensure compliance with all requisite Environmental Permits;

(c) implement procedures to monitor compliance with and to prevent liability under any Environmental Law,

where failure to do so has or is reasonably likely to have a Material Adverse Effect.

23.4 **Environmental Claims**

Each Obligor shall through the Company, promptly upon becoming aware of the same, inform the Agent in writing of:

(a) any Environmental Claim against any member of the Group which is current, pending or threatened; and

(b) any facts or circumstances which are reasonably likely to result in any Environmental Claim being commenced or threatened against any member of the Group,

where the claim, if determined against that member of the Group, has or is reasonably likely to have a Material Adverse Effect.

23.5 **Anti-corruption law**

(a) No Obligor shall (and the Company shall ensure that no other member of the Group will) directly or indirectly use the proceeds of the Facilities for any purpose which would breach the Bribery Act 2010, the United States Foreign Corrupt Practices Act of 1977 or other similar legislation in other jurisdictions.

(b) Each Obligor shall (and the Company shall ensure that each other member of the Group will):

(i) conduct its businesses in compliance with applicable anti-corruption laws; and

(ii) maintain policies and procedures designed to promote and achieve compliance with such laws.

23.6 **Sanctions**

(a) Each Obligor shall (and the Company shall ensure that each member of the Group will) ensure that none of the proceeds of any Utilisation will, directly or indirectly, be used or paid for the purposes of any transaction or business activity related to either:

(i) any person which is listed on a Designated Parties List, or is owned or controlled, directly or indirectly, by any person listed on a Designated Parties List;

(ii) any person that the Obligor knows or has reasonable cause to suspect is acting on behalf of any of the above;

(iii) a governmental agency, authority, or body or state-owned enterprise (or any entity owned or controlled by any of the foregoing) of any country which is the subject of sanctions by any Authority, even if located outside such country;

(iv) a person or entity who is otherwise the target of sanctions by any Authority such that any Finance Party cannot deal or otherwise engage in business transactions with such person or entity; or

(v) any country which is the subject of sanctions by any Authority.

(b) Neither it nor any of its Subsidiaries, nor, to the knowledge of an Obligor, any directors, officers, employees, agents or affiliates of it or any of its Subsidiaries shall engage in, directly or indirectly, any business activity or transaction related to either:

(i) any person which is listed on a Designated Parties List, or is owned or controlled, directly or indirectly, by any person listed on a Designated Parties List; or

(ii) any person that the Obligor or the applicable Affiliate knows or has reasonable cause to suspect is acting on behalf of any of the above; or

(iii) any country which is the subject of sanctions by any Authority.

(c) No Obligor shall engage in any conduct which might reasonably be expected to cause it to become a subject of sanctions by any Authority.

(d) The undertakings contained in paragraphs (a), (b) and (c) above shall not apply to the extent that any such undertaking would breach any provision of Council Regulation EC No. 2271/96, as amended from time to time (known as the "Blocking Regulation"), or any applicable implementing legislation.

23.7 **Taxation**

(a) Each Obligor shall (and the Company shall ensure that each member of the Group will) pay and discharge all Taxes imposed upon it or its assets within the time period allowed without incurring penalties unless and only to the extent that:

(i) such payment is being contested in good faith;

(ii) adequate reserves are being maintained for those Taxes and the costs required to contest them have been disclosed in its latest financial statements delivered to the Agent under Clause 21.1 (*Financial statements*); and

(iii) such payment can be lawfully withheld and failure to pay those Taxes does not have or is not reasonably likely to have a Material Adverse Effect.

(b) No member of the Group may change its residence for Tax purposes.

Restrictions on business focus

23.8 **Merger**

No Obligor shall (and the Company shall ensure that no other member of the Group will) enter into (or agree to enter into) any amalgamation, demerger, merger, consolidation or corporate reconstruction other than any solvent liquidation or reorganisation permitted by paragraph (b) of the definition of Permitted Transaction or any sale, lease, transfer or other disposal permitted pursuant to Clause 23.18 (*Disposals*).

23.9 **Change of business**

The Company shall procure that no substantial change is made to the general nature of the business of the Company, the Obligors or the Group taken as a whole from that carried on by the Group at the Original Effective Date.

23.10 **[Reserved]**

23.11 **Acquisitions**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will):

(i) acquire a company or any shares or securities or a business or undertaking (or, in each case, any interest in any of them); or

(ii) incorporate a company; or

(iii) acquire (including through licensing) any Product, Product line or Intellectual Property of or from any other person.

(b) Paragraph (a) above does not apply to an acquisition of a company, of shares, securities or a business or undertaking (or, in each case, any interest in any of them), the incorporation of a company or the acquisition (including through licensing) of any Product, Product line or Intellectual Property of or from any other person which is:

(i) a Permitted Acquisition;

(ii) a Permitted Joint Venture; or

(iii) contemplated by paragraph (b) of the definition of Permitted Transaction.

23.12 **Joint Ventures**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will):

(i) enter into, invest in or acquire (or agree to acquire) any shares, stocks, securities or other interest in any Joint Venture; or

(ii) transfer any assets or lend to or guarantee or give an indemnity for or give Security for the obligations of a Joint Venture or maintain the solvency of or provide working capital to any Joint Venture (or agree to do any of the foregoing).

(b) Paragraph (a) above does not apply to any acquisition of (or agreement to acquire) any interest in a Joint Venture or transfer of assets (or agreement to transfer assets) to a Joint Venture or loan made to or guarantee given in respect of the obligations of a Joint Venture if such transaction is a Permitted Acquisition, a Permitted Disposal, a Permitted Loan or a Permitted Joint Venture.

23.13 **Holding Companies**

The Company shall not trade, carry on any business, own any assets or incur any liabilities except for:

(a) the provision of administrative services (excluding treasury services) to other members of the Group of a type customarily provided by a holding company to its Subsidiaries;

(b) ownership of shares in its Subsidiaries, intra-Group debit balances, intra-Group credit balances and other credit balances in bank accounts, cash and Cash Equivalent Investments but only if those shares, credit balances, cash and Cash Equivalent Investments are subject to the Transaction Security;

(c) any liabilities under the Transaction Documents to which it is a party and professional fees and administration costs in the ordinary course of business as a holding company; or

(d) any issue of shares pursuant to a Permitted Share Issue,

and this Clause shall prevail if but for this Clause a transaction would otherwise be a Permitted Acquisition, a Permitted Disposal, Permitted Financial Indebtedness, a Permitted Joint Venture, a Permitted Guarantee, a Permitted Loan, Permitted Security or a Permitted Transaction.

23.14 **Dormant Subsidiaries**

(a) No Obligor shall (and the Company shall ensure no other member of the Group will) cause or permit any member of the Group which is a Dormant Subsidiary to cease to satisfy the criteria for a Dormant Subsidiary unless such Dormant Subsidiary becomes an Additional Guarantor in accordance with Clause 26.2 (*Additional Guarantors*).

(b) The Company shall ensure that, at all times, the Dormant Subsidiaries in aggregate do not:

(i) own, legally or beneficially, gross assets or net assets (including, in each case, indebtedness owed to them) which in aggregate represent more than 15% of the gross assets or net assets (including indebtedness owed to it) of the Group on a consolidated basis;

(ii) have liabilities which in aggregate represent more than 15% of the liabilities of the Group on a consolidated basis.

Restrictions on dealing with assets and Security

23.15 **Preservation of assets**

Each Obligor shall (and the Company shall ensure that each other member of the Group will) maintain in good working order and condition (ordinary wear and tear excepted) all of its assets necessary for the conduct of its business.

23.16 **Pari passu ranking**

Each Obligor shall ensure that at all times any unsecured and unsubordinated claims of a Finance Party against it under the Finance Documents rank at least *pari passu* with the claims of all its other unsecured and unsubordinated creditors except those creditors whose claims are mandatorily preferred by laws of general application to companies.

23.17 **Negative pledge**

Except as permitted under paragraph (d) below:

(a) No Obligor shall (and the Company shall ensure that no other member of the Group will) create or permit to subsist any Security over any of its assets.

(b) No Obligor shall (and the Company shall ensure that no other member of the Group will) sell, transfer or otherwise dispose of any of its receivables on recourse terms.

(c) No Obligor shall (and the Company shall ensure that no other member of the Group will):

(i) sell, transfer or otherwise dispose of any of its assets on terms whereby they are or may be leased to or re-acquired by any other member of the Group;

(ii) enter into any arrangement under which money or the benefit of a bank or other account may be applied, set-off or made subject to a combination of accounts; or

(iii) enter into any other preferential arrangement having a similar effect,

in circumstances where the arrangement or transaction is entered into primarily as a method of raising Financial Indebtedness or of financing the acquisition of an asset. An arrangement or transaction referred to in paragraph (b) or in this paragraph (c) is termed "**Quasi-Security**".

(d) No Obligor shall (and the Company shall ensure that no other member of the Group will) enter into any agreement, document, instrument or other arrangement with any person which directly or indirectly prohibits or has the effect of prohibiting any

Obligor from assigning, mortgaging, pledging, or granting a security interest in or upon any Lead Product, any Intellectual Property related thereto, or any agreement (including any in-license), document, instrument or other arrangement relating thereto to, or in favour of, the Finance Parties; provided that this restriction shall apply only to Products (and related Intellectual Property, agreements, documents, instruments and other arrangements) which are Lead Products (or in the case of an acquisition, will become Lead Products immediately when acquired) at the time such agreement, document, instrument or other arrangement would otherwise be entered into.

(e) Paragraphs (a) to (d) above do not apply to any Security or (as the case may be) Quasi-Security, which is:

(i) Permitted Security; or

(ii) given under the Finance Documents.

23.18 **Disposals**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will) enter into a single transaction or a series of transactions (whether related or not) and whether voluntary or involuntary to sell, lease, transfer, licence, surrender, set-off or otherwise dispose of any asset, including tax assets.

(b) Paragraph (a) above does not apply to any sale, lease, transfer or other disposal which is:

(i) a Permitted Disposal; or

(ii) a Permitted Transaction.

Restrictions on movement of cash - cash out

23.19 **Loans or credit**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will) be a creditor in respect of any Financial Indebtedness.

(b) Paragraph (a) above does not apply to:

(i) a Permitted Loan; or

(ii) a Permitted Transaction which is referred to in paragraph (a) of the definition of that term.

23.20 **No guarantees or indemnities**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will) incur or allow to remain outstanding any guarantee, bond or indemnity in respect of any obligation of any person.

(b) Paragraph (a) does not apply to a guarantee which is:

(i) a Permitted Guarantee; or

(ii) a Permitted Transaction which is referred to in paragraph (a) of the definition of that term.

23.21 **Dividends and share redemption**

(a) Except as permitted under paragraph (b) below, the Company shall not (and will ensure that no other member of the Group will):

(i) declare, make or pay any dividend, charge, fee or other distribution (or interest on any unpaid dividend, charge, fee or other distribution) (whether in cash or in kind) on or in respect of its share capital (or any class of its share capital);

(ii) repay or distribute any dividend or share premium reserve; or

(iii) redeem, repurchase, defease, retire or repay any of its share capital or resolve to do so.

(b) Paragraph (a) above does not apply to:

(i) a Permitted Distribution; or

(ii) a Permitted Transaction (other than one referred to in paragraph (c) of the definition of that term).

Restrictions on movement of cash - cash in

23.22 **Financial Indebtedness**

(a) Except as permitted under paragraph (b) below, no Obligor shall (and the Company shall ensure that no other member of the Group will) incur or allow to remain outstanding any Financial Indebtedness.

(b) Paragraph (a) above does not apply to Financial Indebtedness which is:

(i) Permitted Financial Indebtedness; or

(ii) contemplated by paragraph (a) of the definition of Permitted Transaction.

23.23 **Share capital**

No Obligor shall (and the Company shall ensure that no other member of the Group will) issue any shares except pursuant to a Permitted Share Issue.

23.24 **People with Significant Control regime**

Each Obligor shall (and the Company shall ensure that each other member of the Group will):

(a) within the relevant timeframe, comply with any notice it receives pursuant to Part 21A of the Companies Act 2006 from any company incorporated in the United Kingdom whose shares are the subject of the Transaction Security; and

(b) promptly provide the Security Agent with a copy of that notice.

Miscellaneous

23.25 **Insurance**

(a) Each Obligor shall (and the Company shall ensure that each other member of the Group will) maintain insurances on and in relation to its business and assets against those risks and to the extent as is usual for companies carrying on the same or substantially similar business.

(b) All insurances must be with reputable independent insurance companies or underwriters.

23.26 **Pensions**

(a) The Company shall ensure that all pension schemes operated by or maintained for the benefit of members of the Group and/or any of their employees are fully funded on the statutory funding objective under sections 221 and 222 of the Pensions Act 2004 and that no action or omission is taken by any member of the Group in relation to such a pension scheme which has or is reasonably likely to have a Material Adverse Effect (including, the termination or commencement of winding-up proceedings of any such pension scheme or any member of the Group ceasing to employ any member of such a pension scheme).

(b) The Company shall ensure that no member of the Group is or has been at any time an employer (for the purposes of Sections 38 to 51 of the Pensions Act 2004) of an occupational pension scheme which is not a money purchase scheme (both terms as defined in the Pension Schemes Act 1993) or "connected" with or an "associate" of (as those terms are used in Sections 38 or 43 of the Pensions Act 2004) such an employer.

(c) The Company shall deliver to the Agent at such times as those reports are prepared in order to comply with the then current statutory or auditing requirements (as applicable either to the trustees of any relevant schemes or to the Company), actuarial reports in relation to all pension schemes mentioned in paragraph (a) above.

(d) The Company shall promptly notify the Agent of any material change in the rate of contributions to any pension schemes mentioned in paragraph (a) above paid or recommended to be paid (whether by the scheme actuary or otherwise) or required (by law or otherwise).

(e) Each Obligor shall immediately notify the Agent of any investigation or proposed investigation of which it is aware by the Pensions Regulator which may lead to the issue of a Financial Support Direction or a Contribution Notice to any member of the Group.

(f) Each Obligor shall immediately notify the Agent if it receives a Financial Support Direction or a Contribution Notice from the Pensions Regulator.

(g) Each Obligor shall furnish each of the following:

(i) promptly upon a request by the Agent or a Lender, copies of Schedule B (or such other schedule as contains actuarial information) to IRS Form 5500 in respect of each Plan;

(ii) within 5 days after receipt by any Obligor, copies of each notice from the PBGC stating its intention to terminate any Plan or to have a trustee appointed to administer any Plan;

(iii) within 5 days after receipt by any Obligor from the sponsor of a Multiemployer Plan, copies of each notice concerning (A) the imposition of withdrawal liability (as defined in Part I of Subtitle E of Title IV of ERISA) by any such Multiemployer Plan, (B) the reorganisation or termination, within the meaning of Title IV of ERISA, of any such Multiemployer Plan and (C) the estimated amount of any liability incurred, or that reasonably may be expected to be incurred, by any Obligor or ERISA Affiliate in connection with any event described in (A) or (B) above;

(iv) promptly in receipt of any such notice, of the imposition of withdrawal liability or a determination that a Multiemployer Plan is, or is expected to be, in "endangered" or "critical" status, within the meaning of Section 305 of ERISA; or

(v) within 20 days after the date that any Obligor files a notice of intent to terminate any Plan, if such termination would require material additional contributions in order to be considered a standard termination within the meaning of Section 4041(b) of ERISA, a copy of each notice; and

(vi) within 5 days after receipt by an Obligor, copies of any notice asserting liability under ERISA.

(h) Each Obligor must be, and remain, in compliance in all respects with all laws and regulations relating to each of its Plans, where failure to do so would or would be reasonably likely to have a Material Adverse Effect.

(i) Each Obligor must ensure that no event or condition exists at any time in relation to a Plan which is reasonably likely to result in the imposition of a security interest on the assets of any Obligor or which would or would be reasonably likely to have a Material Adverse Effect.

23.27 **Access**

If an Event of Default is continuing, each Obligor shall, and the Company shall ensure that each member of the Group will, permit the Agent and/or the Security Agent free access at all reasonable times and on reasonable notice at the risk and cost of the Obligor to (a) the premises, assets, books, accounts and records of each member of the Group and (b) meet and discuss matters with senior management of the Group.

23.28 **Intellectual Property**

(a) Each Obligor shall and the Company shall procure that each other member of the Group will:

(i) preserve and maintain the subsistence and validity of the material Intellectual Property necessary for its business;

(ii) use reasonable endeavours (including the institution of legal proceedings) to prevent any infringement in any material respect of the material Intellectual Property;

(iii) make registrations and pay all registration fees and taxes necessary to maintain any material Intellectual Property in full force and effect and record its interest in that material Intellectual Property;

(iv) not use or permit the material Intellectual Property to be used in a way or take any step or omit to take any step in respect of that material Intellectual Property which may materially and adversely affect the existence or value of that material Intellectual Property or imperil the right of any member of the Group to use such property; and

(v) not discontinue the use of the material Intellectual Property,

where failure to do so (in the case of paragraphs (i) and (ii) above) or such use, permission to use, omission or discontinuation (in the case of paragraphs (iv) and (v) above) is reasonably likely to have a Material Adverse Effect.

(b) Failure to comply with any part of paragraph (a) above shall not be a breach of this Clause 23.28 to the extent that any dealing with Intellectual Property which would otherwise be a breach of paragraph (a) above is contemplated by paragraph (a) of the definition of Permitted Transaction.

23.29 **Financial assistance**

Each Obligor shall (and the Company shall procure each other member of the Group will) comply in all respects with all relevant financial assistance legislation in relevant jurisdictions including in relation to the execution of the Transaction Security Documents and payment of amounts due under this Agreement.

23.30 **Amendments**

No Obligor shall (and the Company shall ensure that no other member of the Group will) amend, vary, novate, supplement, supersede, waive or terminate any of the Transaction Documents or the constitutional documents of a member of the Group over whose shares or other ownership interests Transaction Security has been granted except:

(a) in accordance with Clause 37 (*Amendments and waivers*); or

(b) in a way which could not be reasonably expected to materially and adversely affect the interests of the Finance Parties under the Finance Documents.

23.31 **Treasury Transactions**

No Obligor shall (and the Company will procure that no other member of the Group will) enter into any Treasury Transaction, other than any Treasury Transaction entered into for the hedging of actual or projected real exposures arising in the ordinary course of trading activities of a member of the Group and not for speculative purposes.

23.32 **Further assurance**

(a) Each Obligor shall (and the Company shall procure that each other member of the Group will) promptly do all such acts or execute all such documents (including assignments, transfers, mortgages, charges, notices and instructions) as the Security Agent may reasonably specify and in such form as the Security Agent may reasonably require (in favour of the Security Agent or its nominee(s)) but subject to the Agreed Security Principles in order to:

(i) perfect or protect the Security created or intended to be created under or evidenced by the Transaction Security Documents (which may include the execution of a mortgage, charge, assignment or other Security over all or any of the assets which are, or are intended to be, the subject of the Transaction Security) or for the exercise of any rights, powers and remedies of the Security Agent or the Finance Parties provided by or pursuant to the Finance Documents or by law;

(ii) confer on the Security Agent or confer on the Finance Parties, Security over any property and assets of that Obligor located in any jurisdiction which is (to the extent permitted by local law) equivalent or similar to the Security intended to be conferred by or pursuant to the Transaction Security Documents; and/or

(iii) facilitate the realisation of the assets which are, or are intended to be, the subject of the Transaction Security.

(b) Each Obligor shall (and the Company shall procure that each other member of the Group will) take all such action as is available to it (including making all filings and registrations) as may be necessary for the purpose of the creation, perfection, protection or maintenance of any Security conferred or intended to be conferred on the Security Agent or the Finance Parties by or pursuant to the Finance Documents.

23.33 **Landlord waivers**

If at any time Group Unrestricted Cash held by the Group is less than the lower of (a) $50,000,000 and (b) the aggregate amount of all Loans then outstanding, the Company shall upon request of the Agent use commercially reasonable efforts for a period of not more than 90 days to procure that landlord consents (in form and substance satisfactory to Agent (acting reasonably)) are delivered to the Agent in respect of each of the US Obligor's leased locations with a restriction to an agreed level in accordance with reasonable local market practice and to the extent that the costs remain proportionate to the benefit to the Secured Parties.

23.34 **Condition subsequent**

The Company shall procure that, within 30 days of the Original Effective Date (or such later date as may be agreed between the Company and the Agent), deposit account control agreements or securities account control agreements, as applicable, are entered into by the Security Agent and the relevant account banks in relation to the bank accounts and securities accounts (other than, in each case, Excluded Accounts) of Orchard Therapeutics North America and bank accounts and securities accounts of any other Group Member to the extent such bank accounts or securities accounts, as applicable, are located in the United States (other than, in each case, Excluded Accounts).

24. EVENTS OF DEFAULT

Each of the events or circumstances set out in this Clause 24 is an Event of Default (save for Clause 24.18 (*Acceleration*)).

24.1 **Non-payment**

An Obligor does not pay on the due date any amount payable pursuant to a Finance Document in the manner in which it is expressed to be payable unless:

(a) its failure to pay is caused by:

(i) administrative or technical error by a bank in the transmission of funds; or

(ii) a Disruption Event; and

(b) payment is made within 4 Business Days of its due date.

24.2 **Financial covenants and other obligations**

Any requirement of Clause 22 (*Financial covenants*) is not satisfied or an Obligor does not comply with the provision of Clause 21.1 (*Financial statements*) and/or Clause 21.2 (*Provision and contents of Compliance Certificate*).

24.3 **Other obligations**

(a) An Obligor does not comply with any provision of the Finance Documents (other than those referred to in Clause 24.1 (*Non-payment*) and Clause 24.2 (*Financial covenants and other obligations*)).

(b) No Event of Default under paragraph (a) above will occur if the failure to comply is capable of remedy and is remedied within 10 Business Days after the earlier of (i) the Agent giving notice to the Company or relevant Obligor and (ii) the Company or an Obligor becoming aware of the failure to comply.

24.4 **Misrepresentation**

(a) Any representation, warranty or statement made or deemed to be made by an Obligor in the Finance Documents or any other document delivered by or on behalf of any Obligor under or in connection with any Finance Document is or proves to have been incorrect or misleading when made or deemed to be made.

(b) No Event of Default under paragraph (a) above will occur if the failure to comply is capable of remedy and is remedied within 10 Business Days after the earlier of (i) the Agent giving notice to the Company or relevant Obligor and (ii) the Company or an Obligor becoming aware of the failure to comply.

24.5 **Cross default**

(a) Any Financial Indebtedness of any member of the Group is not paid when due nor within any originally applicable grace period.

(b) Any Financial Indebtedness of any member of the Group is declared to be or otherwise becomes due and payable prior to its specified maturity as a result of an event of default (however described).

(c) Any commitment for any Financial Indebtedness of any member of the Group is cancelled or suspended by a creditor of any member of the Group as a result of an event of default (however described).

(d) Any creditor of any member of the Group becomes entitled to declare any Financial Indebtedness of any member of the Group due and payable prior to its specified maturity as a result of an event of default (however described).

(e) No Event of Default will occur under this Clause 24.5 if the aggregate amount of Financial Indebtedness or commitment for Financial Indebtedness falling within

paragraphs (a) to (d) above is less than $5,000,000 (or its Base Currency Equivalent).

24.6 **Insolvency**

(a) An Obligor:

(i) is unable or admits inability to pay its debts as they fall due;

(ii) is deemed to, or is declared to, be unable to pay its debts under applicable law

(iii) suspends or threatens to suspend making payments on any of its debts; or

(iv) by reason of actual or anticipated financial difficulties, commences negotiations with one or more of its creditors (excluding any Finance Party in its capacity as such) with a view to rescheduling any of its indebtedness.

(b) A moratorium is declared in respect of any indebtedness of any member of the Group. If a moratorium occurs, the ending of the moratorium will not remedy any Event of Default caused by that moratorium.

(c) With respect to any US Obligor:

(i) the present fair saleable value of the assets of such US Obligor is on the date of determination, lower than the total amount of liabilities (including contingent and unliquidated liabilities) of such US Obligor;

(ii) such US Obligor has unreasonably small capital with which to conduct its business;

(iii) such US Obligor is incurring, intends to incur or believes that it will incur debts beyond its ability to pay as the same become due (whether at maturity or otherwise), or admits in writing its inability to pay its debts as they become due (whether at maturity or otherwise); or

(iv) such US Obligor has entered into any transaction with the intention of hindering, delaying or defrauding any present or future creditor of such US Obligor,

provided that in computing the amount of contingent or unliquidated liabilities at any time, such liabilities will be computed at the amount which, in light of all the facts and circumstances existing at such time, represents the amount that can be reasonably be expected to become an actual or matured liability.

24.7 **Insolvency proceedings**

(a) Any corporate action, legal proceedings or other procedure or step is taken in relation to:

(i) the suspension of payments, a moratorium of any indebtedness, winding-up, dissolution, administration or reorganisation (by way of voluntary arrangement, scheme of arrangement or otherwise) of any Obligor;

(ii) a composition, compromise, assignment or arrangement with any creditor of any Obligor;

(iii) the appointment of a liquidator, receiver, administrative receiver, administrator, compulsory manager or other similar officer in respect of any Obligor or any of its assets; or

(iv) enforcement of any Security over any assets of any Obligor,

or any analogous procedure or step is taken in any jurisdiction.

(b) Paragraph (a) shall not apply to:

(i) any winding-up petition which is frivolous or vexatious and is discharged, stayed or dismissed before it is advertised and in any event within 14 days of commencement; or

(ii) any step or procedure contemplated by paragraph (b) of the definition of Permitted Transaction.

24.8 **Creditors' process**

Any expropriation, attachment, sequestration, distress or execution or any analogous process in any jurisdiction affects any asset or assets of a member of the Group having an aggregate value of $5,000,000 or more and is not discharged within 14 days.

24.9 **Unlawfulness and invalidity**

(a) It is or becomes unlawful for an Obligor to perform any of its obligations under the Finance Documents or any Transaction Security created or expressed to be created or evidenced by the Transaction Security Documents ceases to be effective.

(b) Any obligation or obligations of any Obligor under any Finance Document are not (subject to the Legal Reservations) or cease to be legal, valid, binding or enforceable and the cessation individually or cumulatively materially and adversely affects the interests of the Lenders under the Finance Documents.

(c) Any Finance Document ceases to be in full force and effect or any Transaction Security ceases to be legal, valid, binding, enforceable or effective in any material respect or is alleged by a party to it (other than a Finance Party) to be ineffective in any material respect.

24.10 **Cessation of business**

An Obligor suspends or ceases to carry on (or threatens to suspend or cease to carry on) all or a material part of its business except as a result of a disposal which is a Permitted Disposal or a Permitted Transaction which is contemplated in paragraphs (a) or (b) of the definition of that term.

24.11 **Change of ownership**

An Obligor (other than the Company) ceases to be a wholly-owned Subsidiary of the Company, except as a result of a disposal which is a Permitted Disposal.

24.12 **Audit qualification**

The Company's Auditors qualify the audited annual consolidated financial statements of the Company (other than a going concern qualification based solely on any Obligor having negative profits or a determination that any Obligor has less than 12 months liquidity).

24.13 **Repudiation and rescission of agreements**

An Obligor (or any other relevant party) rescinds or purports to rescind or repudiates or purports to repudiate a Finance Document or any of the Transaction Security or evidences an intention to rescind or repudiate a Finance Document or any Transaction Security.

24.14 **Litigation**

Any litigation, arbitration or administrative proceedings or investigations of, or before, any court, arbitral body or agency are started or threatened, or any judgment or order of a court, arbitral body or agency is made, in relation to the Finance Documents or the transactions contemplated in the Finance Documents or against any member of the Group or its assets which have, or has, or are, or is, reasonably likely to have a Material Adverse Effect.

24.15 **Material adverse change**

Any event or circumstance occurs which has or is reasonably likely to have a Material Adverse Effect.

24.16 **ERISA Event**

The occurrence of one or more ERISA Events that:

(a) results in the imposition of a lien or the incurring of a liability by any Obligor; and

(b) individually or in aggregate would have or would reasonably be expected to have a Material Adverse Effect.

24.17 **US insolvency proceedings**

Any of the following occurs in respect of an Obligor:

(a) it commences a voluntary case or proceeding under any existing or future US Debtor Relief Law; or

(b) an involuntary case under any existing or future US Debtor Relief Law is commenced against it and either (x) the case is not dismissed or stayed within 45 days after commencement of the case or (y) an order for relief is issued.

24.18 **Acceleration**

On and at any time after the occurrence of an Event of Default which is continuing the Agent may, and shall if so directed by the Majority Lenders:

(a) by notice to the Company;

(i) cancel the Total Commitments at which time they shall immediately be cancelled;

(ii) declare that all or part of the Utilisations, together with accrued interest, and all other amounts accrued or outstanding under the Finance Documents be immediately due and payable, at which time they shall become immediately due and payable;

(iii) declare that all or part of the Utilisations be payable on demand, at which time they shall immediately become payable on demand by the Agent on the instructions of the Majority Lenders; and/or

(b) exercise or direct the Security Agent to exercise any or all of its rights, remedies, powers or discretions under the Finance Documents.

24.19 **Acceleration for US insolvency proceedings**

If an Event of Default under Clause 24.19 (*US Insolvency Proceedings*) shall occur in respect of any Obligor, then, in addition to the remedies set forth elsewhere in this Agreement, in the other Finance Documents and under applicable law, and without any notice to any Obligor or any other Person or any act by any Finance Party, (i) the Total Commitments and any obligation of the Lenders to issue guarantees or other financial accommodations hereunder shall automatically terminate and (ii) all principal of the Loans then outstanding, together with accrued interest thereon and all fees and other obligations of the Obligors accrued under the Finance Documents shall immediately become due and payable and Obligors shall be obligated to repay all of such obligations in full, without presentment, demand, protest, or notice of any kind, all of which are expressly waived by each Obligor.

SECTION 9

CHANGES TO PARTIES

25. CHANGES TO THE LENDERS

25.1 Assignments and transfers by the Lenders

(a) Subject to this Clause 25, a Lender (the "**Existing Lender**") may:

(i) assign any of its rights; or

(ii) transfer by novation any of its rights and obligations,

under any Finance Document to another bank or financial institution or to a trust, fund or other entity which is regularly engaged in or established for the purpose of making, purchasing or investing in loans, securities or other financial assets (the "**New Lender**").

25.2 Conditions of assignment or transfer

(a) The consent of the Company is required for an assignment or transfer by an Existing Lender to any entity which is (A) a hedge fund, private equity fund or similar public or private investment vehicle that is routinely engaged in the business of investing in distressed debt or (B) a Competitor, unless such transfer is made at a time when an Event of Default is continuing.

(b) The consent of the Company to an assignment or transfer must not be unreasonably withheld or delayed. The Company will be deemed to have given its consent five Business Days after the Existing Lender has requested it unless consent is expressly refused by the Company within that time.

(c) An assignment or transfer of part of a Lender's participation in any Facility must be in an amount such that the amount of that Lender's remaining participation (when aggregated with its Affiliates' and Related Funds' participation) in respect of Commitments or Utilisations made under the Facilities (taken together) is in minimum amount of $1,000,000;

(d) An assignment will only be effective on:

(i) receipt by the Agent (whether in the Assignment Agreement or otherwise) of written confirmation from the New Lender (in form and substance satisfactory to the Agent) that the New Lender will assume the same obligations to the other Finance Parties and the other Secured Parties as it would have been under if it had been an Original Lender; and

(ii) performance by the Agent of all necessary "know your customer" or other similar checks under all applicable laws and regulations in relation to such assignment to a New Lender, the completion of which the Agent shall promptly notify to the Existing Lender and the New Lender.

(e) A transfer will only be effective if the procedure set out in Clause 25.5 (*Procedure for transfer*) is complied with.

(f) If:

(i) a Lender assigns or transfers any of its rights or obligations under the Finance Documents or changes its Facility Office; and

(ii) as a result of circumstances existing at the date the assignment, transfer or change occurs, an Obligor would be obliged to make a payment to the New Lender or Lender acting through its new Facility Office under Clause 15 (*Increased Costs*),

then the New Lender or Lender acting through its new Facility Office is only entitled to receive payment under that Clause to the same extent as the Existing Lender or Lender acting through its previous Facility Office would have been if the assignment, transfer or change had not occurred. This paragraph (f) shall not apply in respect of an assignment or transfer made in the ordinary course of the primary syndication of any Facility.

(g) Each New Lender, by executing the relevant Transfer Certificate or Assignment Agreement, confirms, for the avoidance of doubt, that the Agent has authority to execute on its behalf any amendment or waiver that has been approved by or on behalf of the requisite Lender or Lenders in accordance with this Agreement on or prior to the date on which the transfer or assignment becomes effective in accordance with this Agreement and that it is bound by that decision to the same extent as the Existing Lender would have been had it remained a Lender.

25.3 **Assignment or transfer fee**

(a) Subject to paragraph (b) below, the New Lender shall, on the date upon which an assignment or transfer takes effect, pay to the Agent (for its own account) a fee of $3,500.

(b) No fee is payable pursuant to paragraph (a) above if:

(i) the Agent agrees that no fee is payable; or

(ii) the assignment or transfer is made by an Existing Lender:

(1) to an Affiliate of that Existing Lender; or

(2) to a fund which is a Related Fund of that Existing Lender.

25.4 **Limitation of responsibility of Existing Lenders**

(a) Unless expressly agreed to the contrary, an Existing Lender makes no representation or warranty and assumes no responsibility to a New Lender for:

(i) the legality, validity, effectiveness, adequacy or enforceability of the Transaction Documents, the Transaction Security or any other documents;

(ii) the financial condition of any Obligor;

(iii) the performance and observance by any Obligor or any other member of the Group of its obligations under the Transaction Documents or any other documents; or

(iv) the accuracy of any statements (whether written or oral) made in or in connection with any Transaction Document or any other document,

and any representations or warranties implied by law are excluded.

(b) Each New Lender confirms to the Existing Lender, the other Finance Parties and the Secured Parties that it:

(i) has made (and shall continue to make) its own independent investigation and assessment of the financial condition and affairs of each Obligor and its related entities in connection with its participation in this Agreement and has not relied exclusively on any information provided to it by the Existing Lender or any other Finance Party in connection with any Transaction Document or the Transaction Security; and

(ii) will continue to make its own independent appraisal of the creditworthiness of each Obligor and its related entities whilst any amount is or may be outstanding under the Finance Documents or any Commitment is in force.

(c) Nothing in any Finance Document obliges an Existing Lender to:

(i) accept a re-transfer or reassignment from a New Lender of any of the rights and obligations assigned or transferred under this Clause 25; or

(ii) support any losses directly or indirectly incurred by the New Lender by reason of the non-performance by any Obligor of its obligations under the Transaction Documents or otherwise.

25.5 **Procedure for transfer**

(a) Subject to the conditions set out in Clause 25.2 (*Conditions of assignment or transfer*) a transfer is effected in accordance with paragraph (b) below when the Agent executes an otherwise duly completed Transfer Certificate delivered to it by the Existing Lender and the New Lender. The Agent shall, subject to paragraph (b) below, as soon as reasonably practicable after receipt by it of a duly completed Transfer Certificate appearing on its face to comply with the terms of this Agreement and delivered in accordance with the terms of this Agreement, execute that Transfer Certificate.

(b) The Agent shall only be obliged to execute a Transfer Certificate delivered to it by the Existing Lender and the New Lender once it is satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations in relation to the transfer to such New Lender.

(c) Subject to Clause 25.9 (*Pro Rata Interest Settlement*) on the Transfer Date:

(i) to the extent that in the Transfer Certificate the Existing Lender seeks to transfer by novation its rights, benefits and obligations under the Finance Documents and in respect of the Transaction Security each of the Obligors and the Existing Lender shall be released from further obligations towards one another under the Finance Documents and in respect of the Transaction Security and their respective rights against one another under the Finance Documents and in respect of the Transaction Security shall be cancelled (being the "**Discharged Rights and Obligations**");

(ii) each of the Obligors and the New Lender shall assume obligations towards one another and/or acquire rights and benefits against one another which differ from the Discharged Rights and Obligations only insofar as that

Obligor or other member of the Group and the New Lender have assumed and/or acquired the same in place of that Obligor and the Existing Lender;

(iii) the Agent, the Arranger, the Security Agent, the New Lender and the other Lenders shall acquire the same rights and assume the same obligations between themselves and in respect of the Transaction Security as they would have acquired and assumed had the New Lender been an Original Lender with the rights, and/or obligations acquired or assumed by it as a result of the transfer and to that extent the Agent, the Arranger and the Security Agent and the Existing Lender shall each be released from further obligations to each other under the Finance Documents; and

(iv) the New Lender shall become a Party as a "Lender".

25.6 **Procedure for assignment**

(a) Subject to the conditions set out in Clause 25.2 (*Conditions of assignment or transfer*) an assignment may be effected in accordance with paragraph (c) below when the Agent executes an otherwise duly completed Assignment Agreement delivered to it by the Existing Lender and the New Lender. The Agent shall, subject to paragraph (b) below, as soon as reasonably practicable after receipt by it of a duly completed Assignment Agreement appearing on its face to comply with the terms of this Agreement and delivered in accordance with the terms of this Agreement, execute that Assignment Agreement.

(b) The Agent shall only be obliged to execute an Assignment Agreement delivered to it by the Existing Lender and the New Lender once it is satisfied it has complied with all necessary "know your customer" or other similar checks under all applicable laws and regulations in relation to the assignment to such New Lender.

(c) Subject to Clause 25.9 (*Pro Rata Interest Settlement*) on the Transfer Date:

(i) the Existing Lender will assign absolutely to the New Lender its rights under the Finance Documents and in respect of the Transaction Security expressed to be the subject of the assignment in the Assignment Agreement;

(ii) the Existing Lender will be released from the obligations (the "**Relevant Obligations**") expressed to be the subject of the release in the Assignment Agreement (and any corresponding obligations by which it is bound in respect of the Transaction Security); and

(iii) the New Lender shall become a Party as a "Lender" and will be bound by obligations equivalent to the Relevant Obligations.

(d) Lenders may utilise procedures other than those set out in this Clause 25.6 to assign their rights under the Finance Documents (but not, without the consent of the relevant Obligor or unless in accordance with Clause 25.5 (*Procedure for transfer*), to obtain a release by that Obligor from the obligations owed to that Obligor by the Lenders nor the assumption of equivalent obligations by a New Lender) provided that they comply with the conditions set out in Clause 25.2 (*Conditions of assignment or transfer*) .

25.7 **Copy of Transfer Certificate, Assignment Agreement or Increase Confirmation to Company**

The Agent shall, as soon as reasonably practicable after it has executed a Transfer Certificate or an Assignment Agreement or Increase Confirmation, send to the Company a copy of that Transfer Certificate or Assignment Agreement or Increase Confirmation.

25.8 **Security Interests over Lenders' rights**

In addition to the other rights provided to Lenders under this Clause 25, each Lender may without consulting with or obtaining consent from any Obligor, at any time charge, assign or otherwise create Security in or over (whether by way of collateral or otherwise) all or any of its rights under any Finance Document to secure obligations of that Lender including, without limitation:

(a) any charge, assignment or other Security to secure obligations to a federal reserve or central bank; and

(b) any charge, assignment or other Security granted to any holders (or trustee or representatives of holders) of obligations owed, or securities issued, by that Lender as security for those obligations or securities,

except that no such charge, assignment or Security shall:

(i) release a Lender from any of its obligations under the Finance Documents or substitute the beneficiary of the relevant charge, assignment or Security for the Lender as a party to any of the Finance Documents; or

(ii) require any payments to be made by an Obligor other than or in excess of, or grant to any person any more extensive rights than, those required to be made or granted to the relevant Lender under the Finance Documents.

25.9 **Pro Rata Interest Settlement**

(a) If the Agent has notified the Lenders that it is able to distribute interest payments on a "pro rata basis" to Existing Lenders and New Lenders then (in respect of any transfer pursuant to Clause 25.5 (*Procedure for transfer*) or any assignment pursuant to Clause 25.6 (*Procedure for assignment*) the Transfer Date of which, in each case, is after the date of such notification and is not on the last day of an Interest Period):

(i) any interest or fees in respect of the relevant participation which are expressed to accrue by reference to the lapse of time shall continue to accrue in favour of the Existing Lender up to but including the Transfer Date ("Accrued Amounts") and shall become due and payable to the Existing Lender (without further interest accruing on them) until the last day of the current Interest Period (or, if the Interest Period is longer than six Months, on the next of the dates which falls at six Monthly intervals after the first day of that Interest Period); and

(ii) the rights assigned or transferred by the Existing Lender will not include the right to the Accrued Amounts so that, for the avoidance of doubt:

(1) when the Accrued Amounts become payable, those Accrued Amounts will be payable for the account of the Existing Lender, and

(2) the amount payable to the New Lender on that date will be the amount which would, but for the application of this Clause 25.9, have been payable to it on that date, but after deduction of the Accrued Amounts.

(b) In this Clause 25.9 references to "Interest Period" shall be construed to include a reference to any other period for accrual of fees.

(c) An Existing Lender which retains the right to the Accrued Amounts pursuant to this Clause 25.9 but which does not have a Commitment shall be deemed not to be a Lender for the purposes of ascertaining whether the agreement of any specified group of Lenders has been obtained to approve any request for a consent, waiver, amendment or other vote of Lenders under the Finance Documents.

26. CHANGES TO THE OBLIGORS

26.1 **Assignment and transfers by Obligors**

No Obligor or any other member of the Group may assign any of its rights or transfer any of its rights or obligations under the Finance Documents.

26.2 **Additional Borrowers**

(a) Subject to compliance with the provisions of paragraphs (c) and (d) of Clause 21.8 (*"Know your customer" checks*), the Company may request that any of its wholly owned Subsidiaries which is not a Dormant Subsidiary becomes a Borrower. That Subsidiary shall become a Borrower if:

(i) all the Lenders approve the addition of that Subsidiary;

(ii) the Company and that Subsidiary deliver to the Agent a duly completed and executed Accession Deed;

(iii) the Subsidiary is (or becomes) a Guarantor prior to becoming a Borrower;

(iv) the Company confirms that no Default is continuing or would occur as a result of that Subsidiary becoming an Additional Borrower; and

(v) the Agent has received all of the documents and other evidence listed in Part 2 of Schedule 2 (*Conditions Precedent*) in relation to that Additional Borrower, each in form and substance satisfactory to the Agent.

(b) The Agent shall notify the Company and the Lenders promptly upon being satisfied that it has received (in form and substance satisfactory to it) all the documents and other evidence referred to in sub-paragraph (a)(v) of this Clause.

(c) The Lenders may impose whatever limitations they deem reasonably necessary on the ability of any Additional Borrower to utilise any Facility.

(d) Other than to the extent that the Majority Lenders notify the Agent in writing to the contrary before the Agent gives the notification described in paragraph (b) above, the Lenders authorise (but do not require) the Agent to give that notification. The Agent shall not be liable for any damages, costs or losses whatsoever as a result of giving any such notification.

26.3 **Resignation of a Borrower**

(a) In this Clause 26.3, Clause 26.5 (*Resignation of a Guarantor*) and Clause 26.7 (*Resignation and release of security on disposal*), "**Third Party Disposal**" means the disposal of an Obligor to a person which is not a member of the Group where that disposal is permitted under Clause 23.18 (*Disposals*) or made with the approval of the Majority Lenders (and the Company has confirmed this is the case).

(b) If a Borrower is the subject of a Third Party Disposal, the Company may request that such Borrower (other than the Company) ceases to be a Borrower by delivering to the Agent a Resignation Letter.

(c) The Agent shall accept a Resignation Letter and notify the Company and the other Finance Parties of its acceptance if:

(i) the Company has confirmed that no Default is continuing or would result from the acceptance of the Resignation Letter;

(ii) the Borrower is under no actual or contingent obligations as a Borrower under any Finance Documents;

(iii) where the Borrower is also a Guarantor (unless its resignation has been accepted in accordance with Clause 26.5 (*Resignation of a Guarantor*)), its obligations in its capacity as Guarantor continue to be legal, valid, binding and enforceable and in full force and effect (subject to the Legal Reservations) and the amount guaranteed by it as a Guarantor is not decreased (and the Company has confirmed this is the case); and

(iv) the Company has confirmed that it shall ensure that any relevant Disposal Proceeds will be applied in accordance with Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*).

(d) Upon notification by the Agent to the Company of its acceptance of the resignation of a Borrower, that company shall cease to be a Borrower and shall have no further rights or obligations under the Finance Documents as a Borrower except that the resignation shall not take effect (and the Borrower will continue to have rights and obligations under the Finance Documents) until the date on which the Third Party Disposal takes effect.

(e) The Agent may, at the cost and expense of the Company, require a legal opinion from counsel to the Agent confirming the matters set out in paragraph (c)(iii) above and the Agent shall be under no obligation to accept a Resignation Letter until it has obtained such opinion in form and substance satisfactory to it.

26.4 **Additional Guarantors**

(a) Subject to compliance with the provisions of paragraphs (c) and (d) of Clause 21.8 (*"Know your customer" checks*), the Company may request that any of its wholly owned subsidiaries become a Guarantor.

(b) The Company shall procure that any other member of the Group which is not a Dormant Subsidiary shall, subject to the Agreed Security Principles, as soon as possible and in any event within 30 days after becoming a member of the Group (or ceasing to be a Dormant Subsidiary), become an Additional Guarantor and grant such Security as the Agent may require.

(c) A member of the Group shall become an Additional Guarantor if:

(i) the Company and the proposed Obligor deliver to the Agent a duly completed and executed Accession Deed; and

(ii) the Agent has received all of the documents and other evidence listed in Part 2 of Schedule 2 (*Conditions Precedent*) in relation to that Additional Obligor, each in form and substance satisfactory to the Agent.

(d) The Agent shall notify the Company and the Lenders promptly upon being satisfied that it has received (in form and substance satisfactory to it) all the documents and other evidence listed in Part 2 of Schedule 2 (*Conditions Precedent*).

(e) If any legal prohibition would prevent or limit a Subsidiary's ability to become an Additional Guarantor and/or to enter into Transaction Security, the Obligors shall use their reasonable endeavours lawfully to overcome the prohibition.

26.5 **Resignation of a Guarantor**

(a) The Company may request that a Guarantor (other than the Company) ceases to be a Guarantor by delivering to the Agent a Resignation Letter if:

(i) that Guarantor is being disposed of by way of a Third Party Disposal (as defined in Clause 26.3 (*Resignation of a Borrower*) and the Company has confirmed this is the case; or

(ii) all the Lenders have consented to the resignation of that Guarantor.

(b) The Agent shall accept a Resignation Letter and notify the Borrower and the Lenders of its acceptance if:

(i) the Company has confirmed that no Default is continuing or would result from the acceptance of the Resignation Letter;

(ii) no payment is due from the Guarantor under Clause 19.1 (*Guarantee and indemnity*);

(iii) where the Guarantor is also a Borrower, it is under no actual or contingent obligations as a Borrower and has resigned and ceased to be a Borrower under Clause 26.3 (*Resignation of a Borrower*); and

(iv) the Company has confirmed that it shall ensure that the Disposal Proceeds will be applied, in accordance with Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*).

(c) The resignation of that Guarantor shall not be effective until the date of the relevant Third Party Disposal at which time that company shall cease to be a Guarantor and shall have no further rights or obligations under the Finance Documents as a Guarantor.

26.6 **Repetition of representations**

Delivery of an Accession Deed constitutes confirmation by the relevant Subsidiary that the representations and warranties referred to in paragraph (d) of Clause 20.34 (*Times when representations made*) are true and correct in relation to it as at the date of delivery as if made by reference to the facts and circumstances then existing.

26.7 **Resignation and release of security on disposal**

If a Borrower or a Guarantor is or is proposed to be the subject of a Third Party Disposal then:

(a) where that Borrower or Guarantor created Transaction Security over any of its assets or business in favour of the Security Agent, or Transaction Security in favour of the Security Agent was created over the shares (or equivalent) of that Borrower or Guarantor, the Security Agent may, at the cost and request of the Company, release those assets, business or shares (or equivalent) and issue certificates of non-crystallisation; and

(b) any resignation of that Borrower or Guarantor and related release of Transaction Security referred to in paragraph (a) above shall become effective only on the making of that disposal.

SECTION 10

THE FINANCE PARTIES

27. ROLE OF THE AGENT AND THE ARRANGER

27.1 **Appointment of the Agent**

(a) Each of the Arranger and the Lenders appoints the Agent to act as its agent under and in connection with the Finance Documents.

(b) Each of the Arranger and the Lenders authorises the Agent to perform the duties, obligations and responsibilities and to exercise the rights, powers, authorities and discretions specifically given to the Agent under or in connection with the Finance Documents together with any other incidental rights, powers, authorities and discretions.

27.2 **Instructions**

(a) The Agent shall:

(i) unless a contrary indication appears in a Finance Document, exercise or refrain from exercising any right, power, authority or discretion vested in it as Agent in accordance with any instructions given to it by:

(1) all Lenders if the relevant Finance Document stipulates the matter is an all Lender decision; and

(2) in all other cases, the Majority Lenders; and

(ii) not be liable for any act (or omission) if it acts (or refrains from acting) in accordance with paragraph (i) above.

(b) The Agent shall be entitled to request instructions, or clarification of any instruction, from the Majority Lenders (or, if the relevant Finance Document stipulates the matter is a decision for any other Lender or group of Lenders, from that Lender or group of Lenders) as to whether, and in what manner, it should exercise or refrain from exercising any right, power, authority or discretion and the Agent may refrain from acting unless and until it receives any such instructions or clarification that it has requested.

(c) Save in the case of decisions stipulated to be a matter for any other Lender or group of Lenders under the relevant Finance Document and unless a contrary indication appears in a Finance Document, any instructions given to the Agent by the Majority Lenders shall override any conflicting instructions given by any other Parties and will be binding on all Finance Parties save for the Security Agent.

(d) The Agent may refrain from acting in accordance with any instructions of any Lender or group of Lenders until it has received any indemnification and/or security that it may in its discretion require (which may be greater in extent than that contained in the Finance Documents and which may include payment in advance) for any cost, loss or liability which it may incur in complying with those instructions.

(e) In the absence of instructions, the Agent may act (or refrain from acting) as it considers to be in the best interest of the Lenders.

(f) The Agent is not authorised to act on behalf of a Lender (without first obtaining that Lender's consent) in any legal or arbitration proceedings relating to any Finance Document. This paragraph (f) shall not apply to any legal or arbitration proceeding relating to the perfection, preservation or protection of rights under the Transaction Security Documents or enforcement of the Transaction Security or Transaction Security Documents.

27.3 **Duties of the Agent**

(a) The Agent's duties under the Finance Documents are solely mechanical and administrative in nature.

(b) Subject to paragraph (c)) below, the Agent shall promptly forward to a Party the original or a copy of any document which is delivered to the Agent for that Party by any other Party.

(c) Without prejudice to Clause 25.7 (*Copy of Transfer Certificate, Assignment Agreement or Increase Confirmation to Company*), paragraph (b) above shall not apply to any Transfer Certificate, any Assignment Agreement or any Increase Confirmation.

(d) Except where a Finance Document specifically provides otherwise, the Agent is not obliged to review or check the adequacy, accuracy or completeness of any document it forwards to another Party.

(e) If the Agent receives notice from a Party referring to this Agreement, describing a Default and stating that the circumstance described is a Default, it shall promptly notify the other Finance Parties. The Agent is not obliged to monitor or enquire whether a Default has occurred.

(f) If the Agent is aware of the non-payment of any principal, interest, commitment fee or other fee payable to a Finance Party (other than the Agent, the Arranger or the Security Agent) under this Agreement it shall promptly notify the other Finance Parties.

(g) The Agent shall have only those duties, obligations and responsibilities expressly specified in the Finance Documents to which it is expressed to be a party (and no others shall be implied).

27.4 **Role of the Arranger**

Except as specifically provided in the Finance Documents, the Arranger has no obligations of any kind to any other Party under or in connection with any Finance Document.

27.5 **No fiduciary duties**

(a) Nothing in any Finance Document constitutes the Agent or the Arranger as a trustee or fiduciary of any other person.

(b) Neither the Agent nor the Arranger shall be bound to account to any Lender for any sum or the profit element of any sum received by it for its own account.

27.6 **Business with the Group**

The Agent and the Arranger may accept deposits from, lend money to and generally engage in any kind of banking or other business with any member of the Group.

27.7 **Rights and discretions**

(a) The Agent may:

(i) rely on any representation, communication, notice or document believed by it to be genuine, correct and appropriately authorised;

(ii) assume that:

(1) any instructions received by it from the Majority Lenders, any Lenders or any group of Lenders are duly given in accordance with the terms of the Finance Documents; and

(2) unless it has received notice of revocation, that those instructions have not been revoked; and

(iii) rely on a certificate from any person:

(1) as to any matter of fact or circumstance which might reasonably be expected to be within the knowledge of that person; or

(2) to the effect that such person approves of any particular dealing, transaction, step, action or thing,

as sufficient evidence that that is the case and, in the case of paragraph (1) above, may assume the truth and accuracy of that certificate.

(b) The Agent may assume (unless it has received notice to the contrary in its capacity as agent for the Lenders) that:

(i) no Default has occurred (unless it has actual knowledge of a Default arising under Clause 24.1 (*Non-payment*));

(ii) any right, power, authority or discretion vested in any Party or any group of Lenders has not been exercised; and

(iii) any notice or request made by the Company (other than a Utilisation Request or Selection Notice) is made on behalf of and with the consent and knowledge of all the Obligors.

(c) The Agent may engage and pay for the advice or services of any lawyers, accountants, tax advisers, surveyors or other professional advisers or experts.

(d) Without prejudice to the generality of paragraph (c) above or paragraph (e) below, the Agent may at any time engage and pay for the services of any lawyers to act as independent counsel to the Agent (and so separate from any lawyers instructed by the Lenders) if the Agent in its reasonable opinion deems this to be desirable.

(e) The Agent may rely on the advice or services of any lawyers, accountants, tax advisers, surveyors or other professional advisers or experts (whether obtained by the Agent or by any other Party) and shall not be liable for any damages, costs or

losses to any person, any diminution in value or any liability whatsoever arising as a result of its so relying.

(f) The Agent may act in relation to the Finance Documents through its officers, employees and agents and the Agent shall not:

(i) be liable for any error of judgment made by any such person; or

(ii) be bound to supervise, or be in any way responsible for any loss incurred by reason of misconduct, omission or default on the part, of any such person,

unless such error or such loss was directly caused by the Agent's gross negligence or wilful misconduct.

(g) Unless a Finance Document expressly provides otherwise the Agent may disclose to any other Party any information it reasonably believes it has received as agent under this Agreement.

(h) Without prejudice to the generality of paragraph (g) above, the Agent:

(i) may disclose; and

(ii) on the written request of the Company or the Majority Lenders shall, as soon as reasonably practicable, disclose,

the identity of a Defaulting Lender to the Company and to the other Finance Parties.

(i) Notwithstanding any other provision of any Finance Document to the contrary, none of the Agent or the Arranger is obliged to do or omit to do anything if it would, or might in its reasonable opinion, constitute a breach of any law or regulation or a breach of a fiduciary duty or duty of confidentiality.

(j) Notwithstanding any provision of any Finance Document to the contrary, the Agent is not obliged to expend or risk its own funds or otherwise incur any financial liability in the performance of its duties, obligations or responsibilities or the exercise of any right, power, authority or discretion if it has grounds for believing the repayment of such funds or adequate indemnity against, or security for, such risk or liability is not reasonably assured to it.

27.8 **Responsibility for documentation**

Neither the Agent or the Arranger is responsible or liable for:

(a) the adequacy, accuracy or completeness of any information (whether oral or written) supplied by the Agent, the Arranger, an Obligor or any other person in or in connection with any Finance Document or the transactions contemplated in the Finance Documents or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document;

(b) the legality, validity, effectiveness, adequacy or enforceability of any Finance Document or the Transaction Security or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Transaction Security; or

(c) any determination as to whether any information provided or to be provided to any Finance Party is non-public information the use of which may be regulated or prohibited by applicable law or regulation relating to insider dealing or otherwise.

27.9 **No duty to monitor**

The Agent shall not be bound to enquire:

(a) whether or not any Default has occurred;

(b) as to the performance, default or any breach by any Party of its obligations under any Finance Document; or

(c) whether any other event specified in any Finance Document has occurred.

27.10 **Exclusion of liability**

(a) Without limiting paragraph (b) below (and without prejudice to any other provision of any Finance Document excluding or limiting the liability of the Agent, the Agent will not be liable (including, without limitation, for negligence or any other category of liability whatsoever) for:

(i) any damages, costs or losses to any person, any diminution in value, or any liability whatsoever arising as a result of taking or not taking any action under or in connection with any Finance Document or the Transaction Security, unless directly caused by its gross negligence or wilful misconduct;

(ii) exercising, or not exercising, any right, power, authority or discretion given to it by, or in connection with, any Finance Document, the Transaction Security or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with, any Finance Document or the Transaction Security; or

(iii) without prejudice to the generality of paragraphs (i) and (ii) above, any damages, costs or losses to any person, any diminution in value or any liability whatsoever arising as a result of:

(1) any act, event or circumstance not reasonably within its control; or

(2) the general risks of investment in, or the holding of assets in, any jurisdiction,

including (in each case and without limitation) such damages, costs, losses, diminution in value or liability arising as a result of: nationalisation, expropriation or other governmental actions; any regulation, currency restriction, devaluation or fluctuation; market conditions affecting the execution or settlement of transactions or the value of assets (including any Disruption Event); breakdown, failure or malfunction of any third party transport, telecommunications, computer services or systems; natural disasters or acts of God; war, terrorism, insurrection or revolution; or strikes or industrial action.

(b) No Party (other than the Agent) may take any proceedings against any officer, employee or agent of the Agent, in respect of any claim it might have against the Agent or in respect of any act or omission of any kind by that officer, employee or

agent in relation to any Finance Document or any Transaction Document and any officer, employee or agent of the Agent may rely on this Clause subject to Clause 1.3 (*Third party rights*) and the provisions of the Third Parties Act.

(c) The Agent will not be liable for any delay (or any related consequences) in crediting an account with an amount required under the Finance Documents to be paid by the Agent if the Agent has taken all necessary steps as soon as reasonably practicable to comply with the regulations or operating procedures of any recognised clearing or settlement system used by the Agent for that purpose.

(d) Nothing in this Agreement shall oblige the Agent or the Arranger to carry out:

(i) any "know your customer" or other checks in relation to any person; or

(ii) any check on the extent to which any transaction contemplated by this Agreement might be unlawful for any Lender or for any Affiliate of any Lender,

on behalf of any Lender and each Lender confirms to the Agent and the Arranger that it is solely responsible for any such checks it is required to carry out and that it may not rely on any statement in relation to such checks made by the Agent or the Arranger.

(e) Without prejudice to any provision of any Finance Document excluding or limiting the Agent's liability, any liability of the Agent arising under or in connection with any Finance Document or the Transaction Security shall be limited to the amount of actual loss which has been finally judicially determined to have been suffered (as determined by reference to the date of default of the Agent or, if later, the date on which the loss arises as a result of such default) but without reference to any special conditions or circumstances known to the Agent at any time which increase the amount of that loss. In no event shall the Agent be liable for any loss of profits, goodwill, reputation, business opportunity or anticipated saving, or for special, punitive, indirect or consequential damages, whether or not the Agent has been advised of the possibility of such loss or damages.

27.11 **Lenders' indemnity to the Agent**

(a) Each Lender shall (in proportion to its share of the Total Commitments or, if the Total Commitments are then zero, to its share of the Total Commitments immediately prior to their reduction to zero) indemnify the Agent, within three Business Days of demand, against any cost, loss or liability (including, without limitation, for negligence or any other category of liability whatsoever) incurred by the Agent (otherwise than by reason of the Agent's gross negligence or wilful misconduct) (or, in the case of any cost, loss or liability pursuant to Clause 31.11 (*Disruption to payment systems etc.*), notwithstanding the Agent's negligence, gross negligence or any other category of liability whatsoever but not including any claim based on the fraud of the Agent) in acting as Agent under the Finance Documents (unless the Agent has been reimbursed by an Obligor pursuant to a Finance Document).

(b) Subject to paragraph (c) below, the Company shall immediately on demand reimburse any Lender for any payment that Lender makes to the Agent pursuant to paragraph (a) above.

(c) Paragraph (b) above shall not apply to the extent that the indemnity payment in respect of which the Lender claims reimbursement relates to a liability of the Agent to an Obligor.

27.12 **Resignation of the Agent**

(a) The Agent may resign and appoint one of its Affiliates as successor by giving notice to the Lenders and the Company.

(b) Alternatively the Agent may resign by giving 30 days' notice to the Lenders and the Company, in which case the Majority Lenders (after consultation with the Company) may appoint a successor Agent.

(c) If the Majority Lenders have not appointed a successor Agent in accordance with paragraph (b) above within 20 days after notice of resignation was given, the retiring Agent (after consultation with the Company) may appoint a successor Agent (acting through an office in the United Kingdom).

(d) If the Agent wishes to resign because (acting reasonably) it has concluded that it is no longer appropriate for it to remain as agent and the Agent is entitled to appoint a successor Agent under paragraph (c) above, the Agent may (if it concludes (acting reasonably) that it is necessary to do so in order to persuade the proposed successor Agent to become a party to this Agreement as Agent) agree with the proposed successor Agent amendments to this Clause 27 and any other term of this Agreement dealing with the rights or obligations of the Agent consistent with then current market practice for the appointment and protection of corporate trustees together with any reasonable amendments to the agency fee payable under this Agreement which are consistent with the successor Agent's normal fee rates and those amendments will bind the Parties.

(e) The retiring Agent shall, at its own cost, make available to the successor Agent such documents and records and provide such assistance as the successor Agent may reasonably request for the purposes of performing its functions as Agent under the Finance Documents.

(f) The Agent's resignation notice shall only take effect upon the appointment of a successor.

(g) Upon the appointment of a successor, the retiring Agent shall be discharged from any further obligation in respect of the Finance Documents (other than its obligations under paragraph (e) above) but shall remain entitled to the benefit of Clause 16.3 (*Indemnity to the Agent*) and this Clause 27 (and any agency fees for the account of the retiring Agent shall cease to accrue from (and shall be payable on) that date). Any successor and each of the other Parties shall have the same rights and obligations amongst themselves as they would have had if such successor had been an original Party.

(h) The Agent shall resign in accordance with paragraph (b) above (and, to the extent applicable, shall use reasonable endeavours to appoint a successor Agent pursuant to paragraph (c) above) if on or after the date which is three months before the earliest FATCA Application Date relating to any payment to the Agent under the Finance Documents, either:

(i) the Agent fails to respond to a request under Clause 14.8 (*FATCA Information*) and the Company or a Lender reasonably believes that the Agent will not be (or will have ceased to be) a FATCA Exempt Party on or after that FATCA Application Date;

(ii) the information supplied by the Agent pursuant to Clause 14.8 (*FATCA Information*) indicates that the Agent will not be (or will have ceased to be) a FATCA Exempt Party on or after that FATCA Application Date; or

(iii) the Agent notifies the Company and the Lenders that the Agent will not be (or will have ceased to be) a FATCA Exempt Party on or after that FATCA Application Date;

and (in each case) the Company or a Lender reasonably believes that a Party will be required to make a FATCA Deduction that would not be required if the Agent were a FATCA Exempt Party, and the Company or that Lender, by notice to the Agent, requires it to resign.

27.13 **Replacement of the Agent**

(a) After consultation with the Company, the Majority Lenders may, by giving 30 days' notice to the Agent (or, at any time whilst the Agent is an Impaired Agent, by giving any shorter notice determined by the Majority Lenders) replace the Agent by appointing a successor Agent (acting through an office in the United Kingdom).

(b) The retiring Agent shall (at its own cost if it is an Impaired Agent and otherwise at the expense of the Lenders) make available to the successor Agent such documents and records and provide such assistance as the successor Agent may reasonably request for the purposes of performing its functions as Agent under the Finance Documents.

(c) The appointment of the successor Agent shall take effect on the date specified in the notice from the Majority Lenders to the retiring Agent. As from this date, the retiring Agent shall be discharged from any further obligation in respect of the Finance Documents (other than its obligations under paragraph (b) above) but shall remain entitled to the benefit of Clause 16.3 (*Indemnity to the Agent*) and this Clause 27 (and any agency fees for the account of the retiring Agent shall cease to accrue from (and shall be payable on) that date).

(d) Any successor Agent and each of the other Parties shall have the same rights and obligations amongst themselves as they would have had if such successor had been an original Party.

27.14 **Confidentiality**

(a) In acting as agent for the Finance Parties, the Agent shall be regarded as acting through its agency division which shall be treated as a separate entity from any other of its divisions or departments.

(b) If information is received by another division or department of the Agent, it may be treated as confidential to that division or department and the Agent shall not be deemed to have notice of it.

27.15 **Relationship with the Lenders**

(a) Subject to Clause 25.9 (*Pro Rata Interest Settlement*), the Agent may treat the person shown in its records as Lender at the opening of business (in the place of the Agent's principal office as notified to the Finance Parties from time to time) as the Lender acting through its Facility Office:

(i) entitled to or liable for any payment due under any Finance Document on that day; and

(ii) entitled to receive and act upon any notice, request, document or communication or make any decision or determination under any Finance Document made or delivered on that day,

unless it has received not less than five Business Days' prior notice from that Lender to the contrary in accordance with the terms of this Agreement.

(b) Any Lender may by notice to the Agent appoint a person to receive on its behalf all notices, communications, information and documents to be made or dispatched to that Lender under the Finance Documents. Such notice shall contain the address, fax number and (where communication by electronic mail or other electronic means is permitted under Clause 33.6 (*Electronic communication*)) electronic mail address and/or any other information required to enable the transmission of information by that means (and, in each case, the department or officer, if any, for whose attention communication is to be made) and be treated as a notification of a substitute address, fax number, electronic mail address (or such other information), department and officer by that Lender for the purposes of Clause 33.2 (*Addresses*) and paragraph (a)(ii) of Clause 33.6 (*Electronic communication*) and the Agent shall be entitled to treat such person as the person entitled to receive all such notices, communications, information and documents as though that person were that Lender.

27.16 **Credit appraisal by the Lenders**

Without affecting the responsibility of any Obligor for information supplied by it or on its behalf in connection with any Finance Document, each Lender confirms to the Agent and the Arranger that it has been, and will continue to be, solely responsible for making its own independent appraisal and investigation of all risks arising under or in connection with any Finance Document including but not limited to:

(a) the financial condition, status and nature of each member of the Group;

(b) the legality, validity, effectiveness, adequacy or enforceability of any Finance Document, the Transaction Security and any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Transaction Security;

(c) whether that Lender has recourse, and the nature and extent of that recourse, against any Party or any of its respective assets under or in connection with any Finance Document, the Transaction Security, the transactions contemplated by the Finance Documents or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Transaction Security;

(d) the adequacy, accuracy or completeness of any information provided by the Agent, any Party or by any other person under or in connection with any Finance Document, the transactions contemplated by any Finance Document or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document; and

(e) the right or title of any person in or to, or the value or sufficiency of any part of the Charged Property, the priority of any of the Transaction Security or the existence of any Security affecting the Charged Property.

27.17 **Deduction from amounts payable by the Agent**

If any Party owes an amount to the Agent under the Finance Documents the Agent may, after giving notice to that Party, deduct an amount not exceeding that amount from any payment to that Party which the Agent would otherwise be obliged to make under the Finance Documents and apply the amount deducted in or towards satisfaction of the amount owed. For the purposes of the Finance Documents that Party shall be regarded as having received any amount so deducted.

27.18 **Reliance and engagement letters**

Each Finance Party and Secured Party confirms that each of the Arranger and the Agent has authority to accept on its behalf (and ratifies the acceptance on its behalf of any letters or reports already accepted by the Arranger or Agent) the terms of any reliance letter or engagement letters relating to any reports or letters provided by accountants in connection with the Finance Documents or the transactions contemplated in the Finance Documents and to bind it in respect of those reports or letters and to sign such letters on its behalf and further confirms that it accepts the terms and qualifications set out in such letters.

27.19 **The Register**

The Agent, acting for this purpose as a non-fiduciary agent of each US Obligor, shall maintain, or cause to be maintained, a register (the "**Register**") for the recordation of the names and addresses of the Lenders and the principal amount of the Facility owing to each Lender pursuant to the terms hereof from time to time (each, a "**Registered Loan**"). Other than in connection with an assignment by a Lender of all or any part of its Commitment to an Affiliate of such Lender or a Related Fund of such Lender (i) a Registered Loan (and the registered note, if any, evidencing the same) may be assigned or sold in whole or in part only by registration of such assignment or sale on the Register (and each registered note shall expressly so provide) and (ii) any assignment or sale of all or part of such Registered Loan (and the registered note, if any, evidencing the same) may be effected only by registration of such assignment or sale on the Register, together with the surrender of the registered note, if any, evidencing the same duly endorsed by (or accompanied by a written instrument of assignment or sale duly executed by) the holder of such registered note, whereupon, at the request of the designated assignee(s) or transferee(s), one or more new registered notes in the same aggregate principal amount shall be issued to the designated assignee(s) or transferee(s). The Obligors, the Agent and the Lenders may treat each person whose name is recorded in the Register pursuant to the terms hereof as a Lender hereunder for all purposes of this Agreement, notwithstanding notice to the contrary. The Register shall be available for inspection by the Obligors and, in respect to its own Loans and Commitments, any Lender at any reasonable time and from time to time upon reasonable prior notice. This Clause shall be construed so that the Loans are at all times maintained in "registered form" within the meaning of Sections 163(f), 871(h)(2) and 881(c)(2) of the Code and any related regulations (and any successor provisions).

28. THE SECURITY AGENT

28.1 **Security Agent as trustee**

(a) The Security Agent declares that it holds the Charged Property on trust for the Secured Parties on the terms contained in this Agreement.

(b) Each of the Finance Parties authorises the Security Agent to perform the duties, obligations and responsibilities and to exercise the rights, powers, authorities and discretions specifically given to the Security Agent under or in connection with the Finance Documents together with any other incidental rights, powers, authorities and discretions.

28.2 **Enforcement Instructions**

(a) The Security Agent may refrain from enforcing the Transaction Security unless instructed otherwise by the Majority Lenders.

(b) Subject to the Transaction Security having become enforceable in accordance with its terms, the Majority Lenders may give or refrain from giving instructions to the Security Agent to enforce or refrain from enforcing the Transaction Security as they see fit.

(c) The Security Agent is entitled to rely on and comply with instructions given in accordance with this Clause 28.2.

(d) If the Transaction Security is being enforced pursuant to this Clause 28.2, the Security Agent shall enforce the Transaction Security in such manner as the Majority Lenders shall instruct or, in the absence of any such instructions, as the Security Agent considers in its discretion to be appropriate.

28.3 **Instructions**

(a) The Security Agent shall:

(i) subject to paragraphs (d) and (e) below, exercise or refrain from exercising any right, power, authority or discretion vested in it as Security Agent in accordance with any instructions given to it by the Majority Lender; and

(ii) not be liable for any act (or omission) if it acts (or refrains from acting) in accordance with paragraph (i) above.

(b) The Security Agent shall be entitled to request instructions, or clarification of any instruction, from the Majority Lenders as to whether, and in what manner, it should exercise or refrain from exercising any right, power, authority or discretion and the Security Agent may refrain from acting unless and until it receives those instructions or that clarification.

(c) Any instructions given to the Security Agent by the Majority Lenders shall override any conflicting instructions given by any other Parties and will be binding on all Secured Parties.

(d) Paragraph (a) above shall not apply:

(i) where a contrary indication appears in this Agreement;

(ii) where this Agreement requires the Security Agent to act in a specified manner or to take a specified action; or

(iii) in respect of any provision which protects the Security Agent's own position in its personal capacity as opposed to its role of Security Agent for the Secured Parties including, without limitation, Clauses 28.8 (*No duty to account*) to Clause 28.13 (*Exclusion of liability*), Clause 28.16 (*Confidentiality*) to Clause 28.22 (*Custodians and nominees*) and Clause 28.25 (*Acceptance of title*) to Clause 28.28 (*Disapplication of Trustee Acts*).

(e) If giving effect to instructions given by the Majority Lenders would (in the Security Agent's opinion) have an effect equivalent to an amendment of this Agreement, the Security Agent shall not act in accordance with those instructions unless consent to it so acting is obtained from each Party (other than the Security Agent) whose consent would have been required in respect of amendment.

(f) In exercising any discretion to exercise a right, power or authority under the Finance Documents where it has not received any instructions as to the exercise of that discretion, the Security Agent shall do so having regard to the interests of all the Secured Parties.

(g) The Security Agent may refrain from acting in accordance with any instructions of the Majority Lenders until it has received any indemnification and/or security that it may in its discretion require (which may be greater in extent than that contained in the Finance Documents and which may include payment in advance) for any cost, loss or liability (together with any applicable VAT) which it may incur in complying with those instructions.

(h) Without prejudice to the remainder of this Clause 28.3, in the absence of instructions, the Security Agent may act (or refrain from acting) as it considers in its discretion to be appropriate.

28.4 **Waiver of rights**

To the extent permitted under applicable law and subject to Clause 28.2 (*Enforcement Instructions*) and Clause 28.29 (*Application of Proceeds*), each of the Secured Parties and the Obligors waives all rights it may otherwise have to require that the Transaction Security be enforced in any particular order or manner or at any particular time or that any amount received or recovered from any person, or by virtue of the enforcement of any of the Transaction Security or of any other security interest, which is capable of being applied in or towards discharge of any of the Obligations is so applied.

28.5 **Enforcement through Security Agent only**

The Secured Parties shall not have any independent power to enforce, or have recourse to, any of the Transaction Security or to exercise any right, power, authority or discretion arising under the Transaction Security Documents except through the Security Agent

28.6 **Duties of the Security Agent**

(a) The Security Agent's duties under the Finance Documents are solely mechanical and administrative in nature.

(b) The Security Agent shall promptly:

(i) forward to the Agent a copy of any document received by the Security Agent from any Obligor under any Finance Document; and

(ii) forward to a Party the original or a copy of any document which is delivered to the Security Agent for that Party by any other Party.

(c) Except where a Finance Document specifically provides otherwise, the Security Agent is not obliged to review or check the adequacy, accuracy or completeness of any document it forwards to another Party.

(d) If the Security Agent receives notice from a Party referring to any Finance Document, describing a Default and stating that the circumstance described is a Default, it shall promptly notify the Finance Parties.

(e) To the extent that a Party (other than the Security Agent) is required to calculate a Common Currency Amount, the Security Agent shall upon a request by that Party, promptly notify that Party of the relevant Security Agent's Spot Rate of Exchange.

(f) The Security Agent shall have only those duties, obligations and responsibilities expressly specified in the Finance Documents to which it is expressed to be a party (and no others shall be implied).

28.7 **No fiduciary duties to Obligors**

Nothing in this Agreement constitutes the Security Agent as an agent, trustee or fiduciary of any Obligor.

28.8 **No duty to account**

The Security Agent shall not be bound to account to any other Secured Party for any sum or the profit element of any sum received by it for its own account.

28.9 **Business with the Group**

The Security Agent may accept deposits from, lend money to and generally engage in any kind of banking or other business with any member of the Group.

28.10 **Rights and discretions**

(a) The Security Agent may:

(i) rely on any representation, communication, notice or document believed by it to be genuine, correct and appropriately authorised;

(ii) assume that:

(1) any instructions received by it from the Majority Lenders are duly given in accordance with the terms of the Finance Documents;

(2) unless it has received notice of revocation, that those instructions have not been revoked; and

(3) if it receives any instructions to act in relation to the Transaction Security, that all applicable conditions under the Finance Documents for so acting have been satisfied; and

(iii) rely on a certificate from any person:

(1) as to any matter of fact or circumstance which might reasonably be expected to be within the knowledge of that person; or

(2) to the effect that such person approves of any particular dealing, transaction, step, action or thing,

as sufficient evidence that that is the case and, in the case of paragraph (1) above, may assume the truth and accuracy of that certificate.

(b) The Security Agent may assume (unless it has received notice to the contrary in its capacity as security trustee for the Secured Parties) that:

(i) no Default has occurred;

(ii) any right, power, authority or discretion vested in any Party or any group of creditors has not been exercised; and

(iii) any notice made by the Company is made on behalf of and with the consent and knowledge of all the Obligors.

(c) The Security Agent may engage and pay for the advice or services of any lawyers, accountants, tax advisers, surveyors or other professional advisers or experts.

(d) Without prejudice to the generality of paragraph (c) above or paragraph (e) below, the Security Agent may at any time engage and pay for the services of any lawyers to act as independent counsel to the Security Agent (and so separate from any lawyers instructed by any other Finance Party) if the Security Agent in its reasonable opinion deems this to be desirable.

(e) The Security Agent may rely on the advice or services of any lawyers, accountants, tax advisers, surveyors or other professional advisers or experts (whether obtained by the Security Agent or by any other Party) and shall not be liable for any damages, costs or losses to any person, any diminution in value or any liability whatsoever arising as a result of its so relying.

(f) The Security Agent, any Receiver and any Delegate may act in relation to the Finance Documents and the Charged Property through its officers, employees and agents and shall not:

(i) be liable for any error of judgment made by any such person; or

(ii) be bound to supervise, or be in any way responsible for any loss incurred by reason of misconduct, omission or default on the part of any such person,

unless such error or such loss was directly caused by the Security Agent's, Receiver's or Delegate's gross negligence or wilful misconduct.

(g) Unless this Agreement expressly specifies otherwise, the Security Agent may disclose to any other Party any information it reasonably believes it has received as security trustee under this Agreement.

(h) Notwithstanding any other provision of any Finance Document to the contrary, the Security Agent is not obliged to do or omit to do anything if it would, or might in its

reasonable opinion, constitute a breach of any law or regulation or a breach of a fiduciary duty or duty of confidentiality.

(i) Notwithstanding any provision of any Finance Document to the contrary, the Security Agent is not obliged to expend or risk its own funds or otherwise incur any financial liability in the performance of its duties, obligations or responsibilities or the exercise of any right, power, authority or discretion if it has grounds for believing the repayment of such funds or adequate indemnity against, or security for, such risk or liability is not reasonably assured to it.

28.11 **Responsibility for documentation**

None of the Security Agent, any Receiver nor any Delegate is responsible or liable for:

(a) the adequacy, accuracy or completeness of any information (whether oral or written) supplied by the Security Agent, a Obligor or any other person in or in connection with any Finance Document or the transactions contemplated in the Finance Documents or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document; or

(b) the legality, validity, effectiveness, adequacy or enforceability of any Finance Document, the Charged Property or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Charged Property; or

(c) any determination as to whether any information provided or to be provided to any Secured Party is non-public information the use of which may be regulated or prohibited by applicable law or regulation relating to insider dealing or otherwise.

28.12 **No duty to monitor**

The Security Agent shall not be bound to enquire:

(a) whether or not any Default has occurred;

(b) as to the performance, default or any breach by any Party of its obligations under any Finance Document; or

(c) whether any other event specified in any Finance Document has occurred.

28.13 **Exclusion of liability**

(a) Without limiting paragraph (b) below (and without prejudice to any other provision of any Finance Document excluding or limiting the liability of the Security Agent, any Receiver or Delegate), none of the Security Agent, any Receiver nor any Delegate will be liable for:

(i) any damages, costs or losses to any person, any diminution in value, or any liability whatsoever arising as a result of taking or not taking any action under or in connection with any Finance Document or the Charged Property unless directly caused by its gross negligence or wilful misconduct;

(ii) exercising or not exercising any right, power, authority or discretion given to it by, or in connection with, any Finance Document, the Charged Property

or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with, any Finance Document or the Charged Property;

(iii) any shortfall which arises on the enforcement or realisation of the Charged Property; or

(iv) without prejudice to the generality of paragraphs (i) to (iii) above, any damages, costs, losses, any diminution in value or any liability whatsoever arising as a result of:

(1) any act, event or circumstance not reasonably within its control; or

(2) the general risks of investment in, or the holding of assets in, any jurisdiction,

including (in each case and without limitation) such damages, costs, losses, diminution in value or liability arising as a result of: nationalisation, expropriation or other governmental actions; any regulation, currency restriction, devaluation or fluctuation; market conditions affecting the execution or settlement of transactions or the value of assets; breakdown, failure or malfunction of any third party transport, telecommunications, computer services or systems; natural disasters or acts of God; war, terrorism, insurrection or revolution; or strikes or industrial action.

(b) No Party (other than the Security Agent, that Receiver or that Delegate (as applicable)) may take any proceedings against any officer, employee or agent of the Security Agent, a Receiver or a Delegate in respect of any claim it might have against the Security Agent, a Receiver or a Delegate or in respect of any act or omission of any kind by that officer, employee or agent in relation to any Finance Document or any Charged Property and any officer, employee or agent of the Security Agent, a Receiver or a Delegate may rely on this Clause subject to Clause 1.3 (*Third party rights*) and the provisions of the Third Parties Act.

(c) Nothing in this Agreement shall oblige the Security Agent to carry out:

(1) any "know your customer" or other checks in relation to any person; or

(2) any check on the extent to which any transaction contemplated by this Agreement might be unlawful for any Finance Party,

on behalf of any Finance Party and each Finance Party confirms to the Security Agent that it is solely responsible for any such checks it is required to carry out and that it may not rely on any statement in relation to such checks made by the Security Agent.

(d) Without prejudice to any provision of any Finance Document excluding or limiting the liability of the Security Agent, any Receiver or Delegate, any liability of the Security Agent, any Receiver or Delegate arising under or in connection with any Finance Document or the Charged Property shall be limited to the amount of actual loss which has been finally judicially determined to have been suffered (as determined by reference to the date of default of the Security Agent, Receiver or Delegate (as the case may be) or, if later, the date on which the loss arises as a result of such default) but without reference to any special conditions or

circumstances known to the Security Agent, Receiver or Delegate (as the case may be) at any time which increase the amount of that loss. In no event shall the Security Agent, any Receiver or Delegate be liable for any loss of profits, goodwill, reputation, business opportunity or anticipated saving, or for special, punitive, indirect or consequential damages, whether or not the Security Agent, Receiver or Delegate (as the case may be) has been advised of the possibility of such loss or damages.

28.14 **Finance Parties' indemnity to the Security Agent**

(a) Each Finance Party shall (in the proportion that the Obligations due to it bear to the aggregate of the Obligations due to all the Finance Parties for the time being (or, if the Obligations due to the Finance Parties are zero, immediately prior to their being reduced to zero)), indemnify the Security Agent and every Receiver and every Delegate, within three Business Days of demand, against any cost, loss or liability incurred by any of them (otherwise than by reason of the relevant Security Agent's, Receiver's or Delegate's gross negligence or wilful misconduct) in acting as Security Agent, Receiver or Delegate under, or exercising any authority conferred under, the Finance Documents (unless the relevant Security Agent, Receiver or Delegate has been reimbursed by a Obligor pursuant to a Finance Document).

(b) Subject to paragraph (c) below, the Company shall immediately on demand reimburse any Finance Party for any payment that Finance Party makes to the Security Agent pursuant to paragraph (a) above.

(c) Paragraph (b) above shall not apply to the extent that the indemnity payment in respect of which the Finance Party claims reimbursement relates to a liability of the Security Agent to a Obligor.

28.15 **Resignation of the Security Agent**

(a) The Security Agent may resign and appoint one of its Affiliates as successor by giving notice to the Finance Parties and the Company.

(b) Alternatively the Security Agent may resign by giving 30 days' notice to the Finance Parties and the Company, in which case the Majority Lenders may appoint a successor Security Agent.

(c) If the Majority Lenders has not appointed a successor Security Agent in accordance with paragraph (b) above within 20 days after notice of resignation was given, the retiring Security Agent (after consultation with the Agent) may appoint a successor Security Agent.

(d) The retiring Security Agent shall, at its own cost, make available to the successor Security Agent such documents and records and provide such assistance as the successor Security Agent may reasonably request for the purposes of performing its functions as Security Agent under the Finance Documents.

(e) The Security Agent's resignation notice shall only take effect upon:

(i) the appointment of a successor; and

(ii) the transfer of all the Charged Property to that successor.

(f) Upon the appointment of a successor, the retiring Security Agent shall be discharged from any further obligation in respect of the Finance Documents (other

than its obligations under paragraph (b) of Clause28.26 (*Winding up of trust*) and paragraph (d) above) but shall remain entitled to the benefit of this Clause 28 and Clause 16.4 (*Indemnity to the Security Agent*) (and any Security Agent fees for the account of the retiring Security Agent shall cease to accrue from (and shall be payable on) that date). Any successor and each of the other Parties shall have the same rights and obligations amongst themselves as they would have had if that successor had been an original Party.

(g) The Majority Lenders may, by notice to the Security Agent, require it to resign in accordance with paragraph (b) above. In this event, the Security Agent shall resign in accordance with paragraph (b) above.

28.16 **Confidentiality**

(a) In acting as trustee for the Secured Parties, the Security Agent shall be regarded as acting through its trustee division which shall be treated as a separate entity from any other of its divisions or departments.

(b) If information is received by another division or department of the Security Agent, it may be treated as confidential to that division or department and the Security Agent shall not be deemed to have notice of it.

(c) Notwithstanding any other provision of any Finance Document to the contrary, the Security Agent is not obliged to disclose to any other person (i) any confidential information or (ii) any other information if the disclosure would, or might in its reasonable opinion, constitute a breach of any law or regulation or a breach of a fiduciary duty.

28.17 **Information from the Company**

The Company shall supply the Security Agent with any information that the Security Agent may reasonably specify as being necessary or desirable to enable the Security Agent to perform its functions as Security Agent.

28.18 **Credit appraisal by the Secured Parties**

Without affecting the responsibility of any Obligor for information supplied by it or on its behalf in connection with any Finance Document, each Secured Party confirms to the Security Agent that it has been, and will continue to be, solely responsible for making its own independent appraisal and investigation of all risks arising under or in connection with any Finance Document including but not limited to:

(a) the financial condition, status and nature of each member of the Group;

(b) the legality, validity, effectiveness, adequacy or enforceability of any Finance Document, the Charged Property and any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Charged Property;

(c) whether that Secured Party has recourse, and the nature and extent of that recourse, against any Party or any of its respective assets under or in connection with any Finance Document, the Charged Property, the transactions contemplated by the Finance Documents or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document or the Charged Property;

(d) the adequacy, accuracy or completeness of any information provided by the Security Agent, any Party or by any other person under or in connection with any Finance Document, the transactions contemplated by any Finance Document or any other agreement, arrangement or document entered into, made or executed in anticipation of, under or in connection with any Finance Document; and

(e) the right or title of any person in or to, or the value or sufficiency of any part of the Charged Property, the priority of any of the Transaction Security or the existence of any Security affecting the Charged Property.

28.19 **Reliance and engagement letters**

The Security Agent may obtain and rely on any certificate or report from any Obligor's auditor and may enter into any reliance letter or engagement letter relating to that certificate or report on such terms as it may consider appropriate (including, without limitation, restrictions on the auditor's liability and the extent to which that certificate or report may be relied on or disclosed).

28.20 **No responsibility to perfect Transaction Security**

The Security Agent shall not be liable for any failure to:

(a) require the deposit with it of any deed or document certifying, representing or constituting the title of any Obligor to any of the Charged Property;

(b) obtain any licence, consent or other authority for the execution, delivery, legality, validity, enforceability or admissibility in evidence of any Finance Document or the Transaction Security;

(c) register, file or record or otherwise protect any of the Transaction Security (or the priority of any of the Transaction Security) under any law or regulation or to give notice to any person of the execution of any Finance Document or of the Transaction Security;

(d) take, or to require any Obligor to take, any step to perfect its title to any of the Charged Property or to render the Transaction Security effective or to secure the creation of any ancillary Security under any law or regulation; or

(e) require any further assurance in relation to any Transaction Security Document.

28.21 **Insurance by Security Agent**

(a) The Security Agent shall not be obliged:

(i) to insure any of the Charged Property;

(ii) to require any other person to maintain any insurance; or

(iii) to verify any obligation to arrange or maintain insurance contained in any Finance Document,

and the Security Agent shall not be liable for any damages, costs or losses to any person as a result of the lack of, or inadequacy of, any such insurance.

(b) Where the Security Agent is named on any insurance policy as an insured party, it shall not be liable for any damages, costs or losses to any person as a result of its

failure to notify the insurers of any material fact relating to the risk assumed by such insurers or any other information of any kind.

28.22 **Custodians and nominees**

The Security Agent may appoint and pay any person to act as a custodian or nominee on any terms in relation to any asset of the trust as the Security Agent may determine, including for the purpose of depositing with a custodian this Agreement or any document relating to the trust created under this Agreement and the Security Agent shall not be responsible for any loss, liability, expense, demand, cost, claim or proceedings incurred by reason of the misconduct, omission or default on the part of any person appointed by it under this Agreement or be bound to supervise the proceedings or acts of any person.

28.23 **Delegation by the Security Agent**

(a) Each of the Security Agent, any Receiver and any Delegate may, at any time, delegate by power of attorney or otherwise to any person for any period, all or any right, power, authority or discretion vested in it in its capacity as such.

(b) That delegation may be made upon any terms and conditions (including the power to sub-delegate) and subject to any restrictions that the Security Agent, that Receiver or that Delegate (as the case may be) may, in its discretion, think fit in the interests of the Secured Parties.

(c) No Security Agent, Receiver or Delegate shall be bound to supervise, or be in any way responsible for any damages, costs or losses incurred by reason of any misconduct, omission or default on the part of, any such delegate or sub-delegate.

28.24 **Additional Security Agents**

(a) The Security Agent may at any time appoint (and subsequently remove) any person to act as a separate trustee or as a co-trustee jointly with it:

(i) if it considers that appointment to be in the interests of the Secured Parties;

(ii) for the purposes of conforming to any legal requirement, restriction or condition which the Security Agent deems to be relevant; or

(iii) for obtaining or enforcing any judgment in any jurisdiction,

and the Security Agent shall give prior notice to the Company and the Finance Parties of that appointment.

(b) Any person so appointed shall have the rights, powers, authorities and discretions (not exceeding those given to the Security Agent under or in connection with the Finance Documents) and the duties, obligations and responsibilities that are given or imposed by the instrument of appointment.

(c) The remuneration that the Security Agent may pay to that person, and any costs and expenses (together with any applicable VAT) incurred by that person in performing its functions pursuant to that appointment shall, for the purposes of this Agreement, be treated as costs and expenses incurred by the Security Agent.

28.25 **Acceptance of title**

The Security Agent shall be entitled to accept without enquiry, and shall not be obliged to investigate, any right and title that any Obligor may have to any of the Charged Property and shall not be liable for, or bound to require any Obligor to remedy, any defect in its right or title.

28.26 **Winding up of trust**

If the Security Agent, with the approval of the Agent, determines that:

(a) all of the Obligations and all other obligations secured by the Security Documents have been fully and finally discharged; and

(b) no Secured Party is under any commitment, obligation or liability (actual or contingent) to make advances or provide other financial accommodation to any Obligor pursuant to the Finance Documents,

then:

(i) the trusts set out in this Agreement shall be wound up and the Security Agent shall release, without recourse or warranty, all of the Transaction Security and the rights of the Security Agent under each of the Security Documents; and

(ii) any Security Agent which has resigned pursuant to Clause 28.15 (*Resignation of the Security Agent*) shall release, without recourse or warranty, all of its rights under each Security Document.

28.27 **Powers supplemental to Trustee Acts**

The rights, powers, authorities and discretions given to the Security Agent under or in connection with the Finance Documents shall be supplemental to the Trustee Act 1925 and the Trustee Act 2000 and in addition to any which may be vested in the Security Agent by law or regulation or otherwise.

28.28 **Disapplication of Trustee Acts**

Section 1 of the Trustee Act 2000 shall not apply to the duties of the Security Agent in relation to the trusts constituted by this Agreement. Where there are any inconsistencies between the Trustee Act 1925 or the Trustee Act 2000 and the provisions of this Agreement, the provisions of this Agreement shall, to the extent permitted by law and regulation, prevail and, in the case of any inconsistency with the Trustee Act 2000, the provisions of this Agreement shall constitute a restriction or exclusion for the purposes of that Act.

28.29 **Application of proceeds**

Subject to Clause 28.30 (*Prospective liabilities*), all amounts from time to time received or recovered by the Security Agent pursuant to the terms of any Finance Document or in connection with the realisation or enforcement of all or any part of the Transaction Security (for the purposes of this Clause 28, the "**Recoveries**") shall be held by the Security Agent on trust to apply them at any time as the Security Agent (in its discretion) sees fit, to the extent permitted by applicable law (and subject to the provisions of this Clause 28), in the following order of priority:

(a) in discharging any sums owing to the Security Agent, any Receiver or any Delegate;

(b) in discharging all costs and expenses incurred by any Finance Party in connection with any realisation or enforcement of the Transaction Security taken in accordance with the terms of this Agreement;

(c) in payment or distribution to the Agent on its own behalf and on behalf of the other Finance Parties for application towards the discharge of the Obligations in accordance with Clause 31 (*Payment mechanics*)

(d) if none of the Obligors are under any further actual or contingent liability under any Finance Document, in payment or distribution to any person to whom the Security Agent is obliged to pay or distribute in priority to any Obligor; and

(e) the balance, if any, in payment or distribution to the relevant Obligor.

28.30 **Prospective liabilities**

Following (i) a Declared Default or (ii) the enforcement of any Transaction Security, the Security Agent may, in its discretion hold any amount of the Recoveries in one or more interest bearing suspense or impersonal accounts in the name of the Security Agent with such financial institution (including itself) as the Security Agent shall think fit (the interest being credited to the relevant account) for so long as the Security Agent shall think fit for later application under Clause 28.29 (*Application of Proceeds*) in respect of:

(a) any sum to any Security Agent, any Receiver or any Delegate; and

(b) any part of the Obligations,

that the Security Agent reasonably considers, in each case, might become due or owing at any time in the future.

28.31 **Investment of Cash Proceeds**

Prior to the application of the proceeds of the Charged Property in accordance with Clause 28.29 (*Application of proceeds*) the Security Agent may, in its discretion, hold all or part of any Cash Proceeds in one or more interest bearing suspense or impersonal accounts in the name of the Security Agent with such financial institution (including itself) and for so long as the Security Agent shall think fit (the interest being credited to the relevant account) pending the application from time to time of those monies in the Security Agent's discretion in accordance with the provisions of this Clause 28.

28.32 **Currency conversion**

For the purpose of, or pending the discharge of, any of the Obligations the Security Agent may convert any moneys received or recovered by the Security Agent (including, without limitation, any Cash Proceeds) from one currency to another, at the Security Agent's Spot Rate of Exchange.

28.33 **Permitted Deductions**

The Security Agent shall be entitled, in its discretion, (a) to set aside by way of reserve amounts required to meet and (b) to make and pay, any deductions and withholdings (on account of Taxes or otherwise) which it is or may be required by any law or regulation to make from any distribution or payment made by it under this Agreement, and to pay all

Taxes which may be assessed against it in respect of any of the Charged Property, or as a consequence of performing its duties or exercising its rights, powers, authorities and discretions, or by virtue of its capacity as Security Agent under any of the Finance Documents or otherwise (other than in connection with its remuneration for performing its duties under this Agreement).

28.34 **Good Discharge**

(a) Any distribution or payment to be made in respect of the Obligations by the Security Agent may be made to the Agent on behalf of the Finance Parties.

(b) Any distribution or payment made as described in paragraph (a) above shall be a good discharge to the extent of that payment by the Security Agent.

(c) The Security Agent is under no obligation to make the payments to the Agent under paragraph (a) above in the same currency as that in which the Obligations owing to the relevant Finance Party are denominated pursuant to the relevant Finance Document.

28.35 **Calculation of Amounts**

For the purpose of calculating any person's share of any amount payable to or by it, the Security Agent shall be entitled to:

(a) notionally convert the Obligations owed to any person into a common base currency (decided in its discretion by the Security Agent), that notional conversion to be made at the spot rate at which the Security Agent is able to purchase the notional base currency with the actual currency of the Obligations owed to that person at the time at which that calculation is to be made; and

(b) assume that all amounts received or recovered as a result of the enforcement or realisation of the Charged Property are applied in discharge of the Obligations in accordance with the terms of the Finance Documents under which those Obligations have arisen.

29. **CONDUCT OF BUSINESS BY THE FINANCE PARTIES**

No provision of any Finance Document will:

(a) interfere with the right of any Finance Party to arrange its affairs (tax or otherwise) in whatever manner it thinks fit;

(b) oblige any Finance Party to investigate or claim any credit, relief, remission or repayment available to it or the extent, order and manner of any claim; or

(c) oblige any Finance Party to disclose any information relating to its affairs (tax or otherwise) or any computations in respect of Tax.

30. **SHARING AMONG THE FINANCE PARTIES**

30.1 **Payments to Finance Parties**

If a Finance Party (a "**Recovering Finance Party**") receives or recovers any amount from an Obligor other than in accordance with Clause 31 (*Payment mechanics*) (a "**Recovered Amount**") and applies that amount to a payment due under the Finance Documents then:

(a) the Recovering Finance Party shall, within three Business Days, notify details of the receipt or recovery, to the Agent;

(b) the Agent shall determine whether the receipt or recovery is in excess of the amount the Recovering Finance Party would have been paid had the receipt or recovery been received or made by the Agent and distributed in accordance with Clause 31 (*Payment mechanics*), without taking account of any Tax which would be imposed on the Agent in relation to the receipt, recovery or distribution; and

(c) the Recovering Finance Party shall, within three Business Days of demand by the Agent, pay to the Agent an amount (the "**Sharing Payment**") equal to such receipt or recovery less any amount which the Agent determines may be retained by the Recovering Finance Party as its share of any payment to be made, in accordance with Clause 31.6 (*Partial payments*).

30.2 **Redistribution of payments**

The Agent shall treat the Sharing Payment as if it had been paid by the relevant Obligor and distribute it between the Finance Parties (other than the Recovering Finance Party) (the "**Sharing Finance Parties**") in accordance with Clause 31.6 (*Partial payments*) towards the obligations of that Obligor to the Sharing Finance Parties.

30.3 **Recovering Finance Party's rights**

On a distribution by the Agent under Clause 30.2 (*Redistribution of payments*), of a payment received by a Recovering Finance Party from an Obligor, as between the relevant Obligor and the Recovering Finance Party, an amount of the Recovered Amount equal to the Sharing Payment will be treated as not having been paid by that Obligor.

30.4 **Reversal of redistribution**

If any part of the Sharing Payment received or recovered by a Recovering Finance Party becomes repayable and is repaid by that Recovering Finance Party, then:

(a) each Sharing Finance Party shall, upon request of the Agent, pay to the Agent for the account of that Recovering Finance Party an amount equal to the appropriate part of its share of the Sharing Payment (together with an amount as is necessary to reimburse that Recovering Finance Party for its proportion of any interest on the Sharing Payment which that Recovering Finance Party is required to pay) (the "**Redistributed Amount**"); and

(b) as between the relevant Obligor and each relevant Sharing Finance Party, an amount equal to the relevant Redistributed Amount will be treated as not having been paid by that Obligor.

30.5 **Exceptions**

(a) This Clause 30 shall not apply to the extent that the Recovering Finance Party would not, after making any payment pursuant to this Clause, have a valid and enforceable claim against the relevant Obligor.

(b) A Recovering Finance Party is not obliged to share with any other Finance Party any amount which the Recovering Finance Party has received or recovered as a result of taking legal or arbitration proceedings, if:

(i) it notified the other Finance Party of the legal or arbitration proceedings; and

(ii) the other Finance Party had an opportunity to participate in those legal or arbitration proceedings but did not do so as soon as reasonably practicable having received notice and did not take separate legal or arbitration proceedings.

SECTION 11

ADMINISTRATION

31. PAYMENT MECHANICS

31.1 Payments to the Agent

(a) On each date on which an Obligor or a Lender is required to make a payment under a Finance Document, that Obligor or Lender shall make the same available to the Agent (unless a contrary indication appears in a Finance Document) for value on the due date at the time and in such funds specified by the Agent as being customary at the time for settlement of transactions in the relevant currency in the place of payment.

(b) Payment shall be made to such account in the principal financial centre of the country of that currency and with such bank as the Agent, in each case, specifies.

31.2 Distributions by the Agent

Each payment received by the Agent under the Finance Documents for another Party shall, subject to Clause 31.3 (*Distributions to an Obligor*) and Clause 31.4 (*Clawback and pre-funding*) be made available by the Agent as soon as practicable after receipt to the Party entitled to receive payment in accordance with this Agreement (in the case of a Lender, for the account of its Facility Office), to such account as that Party may notify to the Agent by not less than five Business Days' notice with a bank specified by that Party in the principal financial centre of the country of that currency.

31.3 Distributions to an Obligor

The Agent may (with the consent of the Obligor or in accordance with Clause 32 (*Set-Off*)) apply any amount received by it for that Obligor in or towards payment (on the date and in the currency and funds of receipt) of any amount due from that Obligor under the Finance Documents or in or towards purchase of any amount of any currency to be so applied.

31.4 Clawback and pre-funding

(a) Where a sum is to be paid to the Agent under the Finance Documents for another Party, the Agent is not obliged to pay that sum to that other Party (or to enter into or perform any related exchange contract) until it has been able to establish to its satisfaction that it has actually received that sum.

(b) Unless paragraph (c) below applies, if the Agent pays an amount to another Party and it proves to be the case that the Agent had not actually received that amount, then the Party to whom that amount (or the proceeds of any related exchange contract) was paid by the Agent shall on demand refund the same to the Agent together with interest on that amount from the date of payment to the date of receipt by the Agent, calculated by the Agent to reflect its cost of funds.

(c) If the Agent has notified the Lenders that it is willing to make available amounts for the account of a Borrower before receiving funds from the Lenders then if and to the extent that the Agent does so but it proves to be the case that it does not then receive funds from a Lender in respect of a sum which it paid to a Borrower:

(i) the Agent shall notify the Company of that Lender's identity and the Borrower to whom that sum was made available shall on demand refund it to the Agent; and

(ii) the Lender by whom those funds should have been made available or, if that Lender fails to do so, the Borrower to whom that sum was made available, shall on demand pay to the Agent the amount (as certified by the Agent) which will indemnify the Agent against any funding cost incurred by it as a result of paying out that sum before receiving those funds from that Lender.

31.5 **Impaired Agent**

(a) If, at any time, the Agent becomes an Impaired Agent, an Obligor or a Lender which is required to make a payment under the Finance Documents to the Agent in accordance with Clause 31.1 (*Payments to the Agent*) may instead either:

(i) pay that amount direct to the required recipient(s); or

(ii) if in its absolute discretion it considers that it is not reasonably practicable to pay that amount direct to the required recipient(s), pay that amount or the relevant part of that amount to an interest-bearing account held with an Acceptable Bank within the meaning of paragraph (a) of the definition of "Acceptable Bank" and in relation to which no Finance Party Insolvency Event has occurred and is continuing, in the name of the Obligor or the Lender making the payment (the "**Paying Party**") and designated as a trust account for the benefit of the Party or Parties beneficially entitled to that payment under the Finance Documents (the "**Recipient Party**" or "**Recipient Parties**").

In each case such payments must be made on the due date for payment under the Finance Documents.

(b) All interest accrued on the amount standing to the credit of the trust account shall be for the benefit of the Recipient Party or the Recipient Parties *pro rata* to their respective entitlements.

(c) A Party which has made a payment in accordance with this Clause 31.5 shall be discharged of the relevant payment obligation under the Finance Documents and shall not take any credit risk with respect to the amounts standing to the credit of the trust account.

(d) Promptly upon the appointment of a successor Agent in accordance with Clause 27.13 (*Replacement of the Agent*), each Paying Party shall (other than to the extent that that Party has given an instruction pursuant to paragraph (e) below) give all requisite instructions to the bank with whom the trust account is held to transfer the amount (together with any accrued interest) to the successor Agent for distribution to the relevant Recipient Party or Recipient Parties in accordance with Clause 31.2 (*Distributions by the Agent*).

(e) A Paying Party shall, promptly upon request by a Recipient Party and to the extent:

(i) that it has not given an instruction pursuant to paragraph (d) above; and

(ii) that it has been provided with the necessary information by that Recipient Party,

give all requisite instructions to the bank with whom the trust account is held to transfer the relevant amount (together with any accrued interest) to that Recipient Party.

31.6 **Partial payments**

(a) If the Agent receives a payment for application against amounts due in respect of any Finance Documents that is insufficient to discharge all the amounts then due and payable by an Obligor under those Finance Documents, the Agent shall apply that payment towards the obligations of that Obligor under those Finance Documents in the following order:

(i) **first**, in or towards payment *pro rata* of any unpaid amount owing to the Agent or the Security Agent under the Finance Documents;

(ii) **secondly**, in or towards payment *pro rata* of any accrued interest, fee or commission due but unpaid under those Finance Documents;

(iii) **thirdly**, in or towards payment *pro rata* of any principal due but unpaid under those Finance Documents; and

(iv) **fourthly**, in or towards payment *pro rata* of any other sum due but unpaid under the Finance Documents.

(b) The Agent shall, if so directed by the Majority Lenders, vary the order set out in paragraphs (a)(ii) to (a)(iv) above.

(c) Paragraphs (a) and (b) above will override any appropriation made by an Obligor.

31.7 **Set-off by Obligors**

All payments to be made by an Obligor under the Finance Documents shall be calculated and be made without (and free and clear of any deduction for) set-off or counterclaim.

31.8 **Business Days**

(a) Any payment under the Finance Documents which is due to be made on a day that is not a Business Day shall be made on the next Business Day in the same calendar month (if there is one) or the preceding Business Day (if there is not).

(b) During any extension of the due date for payment of any principal or Unpaid Sum under this Agreement interest is payable on the principal or Unpaid Sum at the rate payable on the original due date.

31.9 **Currency of account**

(a) Subject to paragraphs (b) to (e) below, the Base Currency is the currency of account and payment for any sum due from an Obligor under any Finance Document.

(b) A repayment of a Utilisation or Unpaid Sum or a part of a Utilisation or Unpaid Sum shall be made in the currency in which that Utilisation or Unpaid Sum is denominated, pursuant to this Agreement, on its due date.

(c) Each payment of interest shall be made in the currency in which the sum in respect of which the interest is payable was denominated, pursuant to this Agreement, when that interest accrued.

(d) Each payment in respect of costs, expenses or Taxes shall be made in the currency in which the costs, expenses or Taxes are incurred.

(e) Any amount expressed to be payable in a currency other than the Base Currency shall be paid in that other currency.

31.10 **Change of currency**

(a) Unless otherwise prohibited by law, if more than one currency or currency unit are at the same time recognised by the central bank of any country as the lawful currency of that country, then:

(i) any reference in the Finance Documents to, and any obligations arising under the Finance Documents in, the currency of that country shall be translated into, or paid in, the currency or currency unit of that country designated by the Agent (after consultation with the Company); and

(ii) any translation from one currency or currency unit to another shall be at the official rate of exchange recognised by the central bank for the conversion of that currency or currency unit into the other, rounded up or down by the Agent (acting reasonably).

(b) If a change in any currency of a country occurs, this Agreement will, to the extent the Agent (acting reasonably and after consultation with the Company) specifies to be necessary, be amended to comply with any generally accepted conventions and market practice in the Relevant Market and otherwise to reflect the change in currency.

31.11 **Disruption to payment systems etc.**

If either the Agent determines (in its discretion) that a Disruption Event has occurred or the Agent is notified by the Company that a Disruption Event has occurred:

(a) the Agent may, and shall if requested to do so by the Company, consult with the Company with a view to agreeing with the Company such changes to the operation or administration of the Facilities as the Agent may deem necessary in the circumstances;

(b) the Agent shall not be obliged to consult with the Company in relation to any changes mentioned in paragraph (a) above if, in its opinion, it is not practicable to do so in the circumstances and, in any event, shall have no obligation to agree to such changes;

(c) the Agent may consult with the Finance Parties in relation to any changes mentioned in paragraph (a) above but shall not be obliged to do so if, in its opinion, it is not practicable to do so in the circumstances;

(d) any such changes agreed upon by the Agent and the Company shall (whether or not it is finally determined that a Disruption Event has occurred) be binding upon the Parties as an amendment to (or, as the case may be, waiver of) the terms of the

Finance Documents notwithstanding the provisions of Clause 37 (*Amendments and Waivers*);

(e) the Agent shall not be liable for any damages, costs or losses to any person, any diminution in value or any liability whatsoever (including, without limitation for negligence, gross negligence or any other category of liability whatsoever but not including any claim based on the fraud of the Agent) arising as a result of its taking, or failing to take, any actions pursuant to or in connection with this Clause 31.11; and

(f) the Agent shall notify the Finance Parties of all changes agreed pursuant to paragraph (d) above.

32. SET-OFF

A Finance Party may, at any time following an Event of Default which is continuing, set off any matured obligation due from an Obligor under the Finance Documents (to the extent beneficially owned by that Finance Party) against any matured obligation owed by that Finance Party to that Obligor, regardless of the place of payment, booking branch or currency of either obligation. If the obligations are in different currencies, the Finance Party may convert either obligation at a market rate of exchange in its usual course of business for the purpose of the set-off. No security interest is created by this Clause 32.

33. NOTICES

33.1 **Communications in writing**

Any communication to be made under or in connection with the Finance Documents shall be made in writing and, unless otherwise stated, may be made by fax or letter.

33.2 **Addresses**

The address and fax number (and the department or officer, if any, for whose attention the communication is to be made) of each Party for any communication or document to be made or delivered under or in connection with the Finance Documents is:

(a) in the case of the Company, that identified with its name below;

(b) in the case of each Lender or any other Obligor, that notified in writing to the Agent on or prior to the date on which it becomes a Party; and

(c) in the case of the Agent or the Security Agent, that identified with its name below,

or any substitute address, fax number or department or officer as the Party may notify to the Agent (or the Agent may notify to the other Parties, if a change is made by the Agent) by not less than five Business Days' notice.

33.3 **Delivery**

(a) Any communication or document made or delivered by one person to another under or in connection with the Finance Documents will only be effective:

(i) if by way of fax, when received in legible form; or

(ii) if by way of letter, when it has been left at the relevant address or five Business Days after being deposited in the post postage prepaid in an envelope addressed to it at that address,

and, if a particular department or officer is specified as part of its address details provided under Clause 33.2 (*Addresses*), if addressed to that department or officer.

(b) Any communication or document to be made or delivered to the Agent or the Security Agent will be effective only when actually received by the Agent or Security Agent and then only if it is expressly marked for the attention of the department or officer identified with the Agent's or Security Agent's signature below (or any substitute department or officer as the Agent or Security Agent shall specify for this purpose).

(c) All notices from or to an Obligor shall be sent through the Agent.

(d) Any communication or document made or delivered to the Company in accordance with this Clause 33.3 will be deemed to have been made or delivered to each of the Obligors or any other member of the Group party to a Finance Document.

(e) Any communication or document which becomes effective, in accordance with paragraphs (a) to (d) above, after 5:00 pm in the place of receipt shall be deemed only to become effective on the following day.

33.4 **Notification of address and fax number**

Promptly upon changing its address or fax number, the Agent shall notify the other Parties.

33.5 **Communication when Agent is Impaired Agent**

If the Agent is an Impaired Agent the Parties may, instead of communicating with each other through the Agent, communicate with each other directly and (while the Agent is an Impaired Agent) all the provisions of the Finance Documents which require communications to be made or notices to be given to or by the Agent shall be varied so that communications may be made and notices given to or by the relevant Parties directly. This provision shall not operate after a replacement Agent has been appointed.

33.6 **Electronic communication**

(a) Any communication to be made between any two Parties under or in connection with the Finance Documents may be made by electronic mail or other electronic means (including, without limitation, by way of posting to a secure website) if those two Parties:

(i) notify each other in writing of their electronic mail address and/or any other information required to enable the transmission of information by that means; and

(ii) notify each other of any change to their address or any other such information supplied by them by not less than five Business Days' notice.

(b) Any such electronic communication as specified in paragraph (a) above to be made between an Obligor and a Finance Party may only be made in that way to the extent that those two Parties agree that, unless and until notified to the contrary, this is to be an accepted form of communication.

(c) Any such electronic communication as specified in paragraph (a) above made between any two Parties will be effective only when actually received (or made available) in readable form and in the case of any electronic communication made by a Party to the Agent or the Security Agent only if it is addressed in such a manner as the Agent or Security Agent shall specify for this purpose.

(d) Any electronic communication which becomes effective, in accordance with paragraph (c) above, after 5:00 pm in the place in which the Party to whom the relevant communication is sent or made available has its address for the purpose of this Agreement shall be deemed only to become effective on the following day.

(e) Any reference in a Finance Document to a communication being sent or received shall be construed to include that communication being made available in accordance with this Clause 33.6.

33.7 **Use of websites**

(a) The Company may satisfy its obligation under this Agreement to deliver any information in relation to those Lenders (the "**Website Lenders**") who accept this method of communication by posting this information onto an electronic website designated by the Company and the Agent (the "**Designated Website**") if:

(i) the Agent expressly agrees (after consultation with each of the Lenders) that it will accept communication of the information by this method;

(ii) both the Company and the Agent are aware of the address of and any relevant password specifications for the Designated Website; and

(iii) the information is in a printable format or otherwise capable of being downloaded by the relevant Website Lender and is in a format previously agreed between the Company and the Agent.

If any Lender (a "**Paper Form Lender**") does not agree to the delivery of information electronically then the Agent shall notify the Company accordingly and the Company shall at its own cost supply the information to the Agent (in sufficient copies for each Paper Form Lender) in paper form. In any event the Company shall at its own cost supply the Agent with at least one copy in paper form of any information required to be provided by it.

(b) The Agent shall supply each Website Lender with the address of and any relevant password specifications for the Designated Website following designation of that website by the Company and the Agent.

(c) The Company shall promptly upon becoming aware of its occurrence notify the Agent if:

(i) the Designated Website cannot be accessed due to technical failure;

(ii) the password specifications for the Designated Website change;

(iii) any new information which is required to be provided under this Agreement is posted onto the Designated Website;

(iv) any existing information which has been provided under this Agreement and posted onto the Designated Website is amended; or

(v) the Company becomes aware that the Designated Website or any information posted onto the Designated Website is or has been infected by any electronic virus or similar software.

If the Company notifies the Agent under sub-paragraph (c)(i) or sub-paragraph (c)(v) above, all information to be provided by the Company under this Agreement after the date of that notice shall be supplied in paper form unless and until the Agent and each Website Lender is satisfied that the circumstances giving rise to the notification are no longer continuing.

(d) Any Website Lender may request, through the Agent, one paper copy of any information required to be provided under this Agreement which is posted onto the Designated Website. The Company shall at its own cost comply with any such request within ten Business Days.

33.8 **English language**

(a) Any notice given under or in connection with any Finance Document must be in English.

(b) All other documents provided under or in connection with any Finance Document must be:

(i) in English; or

(ii) if not in English, and if so required by the Agent, accompanied by a certified English translation and, in this case, the English translation will prevail unless the document is a constitutional, statutory or other official document.

34. CALCULATIONS AND CERTIFICATES

34.1 **Accounts**

In any litigation or arbitration proceedings arising out of or in connection with a Finance Document, the entries made in the accounts maintained by a Finance Party are prima facie evidence of the matters to which they relate.

34.2 **Certificates and determinations**

Any certification or determination by a Finance Party of a rate or amount under any Finance Document is, in the absence of manifest error, conclusive evidence of the matters to which it relates.

34.3 **Day count convention**

Any interest, commission or fee accruing under a Finance Document will accrue from day to day and is calculated on the basis of the actual number of days elapsed and a year of 360 days or, in any case where the practice in the Relevant Market differs, in accordance with that market practice.

35. PARTIAL INVALIDITY

If, at any time, any provision of any Finance Document is or becomes illegal, invalid or unenforceable in any respect under any law of any jurisdiction, neither the legality, validity or enforceability of the remaining provisions nor the legality, validity or enforceability of such provision under the law of any other jurisdiction will in any way be affected or impaired.

36. REMEDIES AND WAIVERS

No failure to exercise, nor any delay in exercising, on the part of any Finance Party or Secured Party, any right or remedy under a Finance Document shall operate as a waiver of any such right or remedy or constitute an election to affirm any Finance Document. No election to affirm any Finance Document on the part of any Finance Party or Secured Party shall be effective unless it is in writing. No single or partial exercise of any right or remedy shall prevent any further or other exercise or the exercise of any other right or remedy. The rights and remedies provided in each Finance Document are cumulative and not exclusive of any rights or remedies provided by law.

37. AMENDMENTS AND WAIVERS

37.1 **Required consents**

(a) Subject to Clause 37.2 (*All Lender matters*) and Clause 37.3 (*Other exceptions*), any term of the Finance Documents may be amended or waived only with the consent of the Majority Lenders and the Company and any such amendment or waiver will be binding on all Parties.

(b) The Agent may effect, on behalf of any Finance Party, any amendment or waiver permitted by this Clause 37.

(c) Without prejudice to the generality of paragraphs (c), (d) and (e) of Clause 27.7 (*Rights and discretions*), the Agent may engage, pay for and rely on the services of lawyers in determining the consent level required for and effecting any amendment, waiver or consent under this Agreement.

(d) Each Obligor agrees to any such amendment or waiver permitted by this Clause 37 which is agreed to by the Company. This includes any amendment or waiver which would, but for this paragraph (d), require the consent of all of the Guarantors.

(e) Paragraph (c) of Clause 25.9 (*Pro Rata Interest Settlement*) shall apply to this Clause 37.

37.2 **All Lender matters**

Subject to Clause 37.4 (*Changes to reference rates*), an amendment, waiver or (in the case of a Transaction Security Document) a consent of, or in relation to, any term of any Finance Document that has the effect of changing or which relates to:

(a) the definition of "**Majority Lenders**" in Clause 1.1 (*Definitions*);

(b) an extension to the date of payment of any amount under the Finance Documents;

(c) a reduction in the Margin or a reduction in the amount of any payment of principal, interest, fees or commission payable;

(d) a change in currency of payment of any amount under the Finance Documents;

(e) an increase in any Commitment or the Total Commitments, an extension of any Availability Period or any requirement that a cancellation of Commitments reduces the Commitments of the Lenders rateably under the relevant Facility;

(f) a change to the Borrowers or Guarantors other than in accordance with Clause 26 (*Changes to the Obligors*);

(g) any provision which expressly requires the consent of all the Lenders;

(h) Clause 2.3 (*Finance Parties' rights and obligations*), Clause 5.1 (*Delivery of a Utilisation Request*), Clause 7.1 (*Illegality*), the definition of "Change of Control" in Clause 1.1 (*Definitions*), Clause 9.8 (*Application of prepayments*), Clause 25 (*Changes to the Lenders*), Clause 26 (*Changes to the Obligors*) this Clause 37, Clause 42 (*Governing law*) or Clause 43.1 (*Jurisdiction of English courts*);

(i) (other than as expressly permitted by the provisions of any Finance Document) the nature or scope of:

(i) the guarantee and indemnity granted under Clause 19 (*Guarantee and indemnity*);

(ii) the Charged Property; or

(iii) the manner in which the proceeds of enforcement of the Transaction Security are distributed

(except in the case of paragraphs (ii) and (iii) above, insofar as it relates to a sale or disposal of an asset which is the subject of the Transaction Security where such sale or disposal is expressly permitted under this Agreement or any other Finance Document); or

(j) the release of any guarantee and indemnity granted under Clause 19 (*Guarantee and indemnity*) or of any Transaction Security unless permitted under this Agreement or any other Finance Document or relating to a sale or disposal of an asset which is the subject of the Transaction Security where such sale or disposal is permitted under this Agreement or any other Finance Document,

shall not be made, or given, without the prior consent of all the Lenders.

37.3 **Other exceptions**

An amendment or waiver which relates to the rights or obligations of the Agent, the Arranger or the Security Agent (each in their capacity as such) may not be effected without the consent of the Agent, the Arranger or the Security Agent, as the case may be.

37.4 **Changes to reference rates**

Subject to Clause 37.3 (*Other exceptions*), if a Published Rate Replacement Event has occurred in relation to any Published Rate, any amendment or waiver which relates to:

(a) providing for the use of a Replacement Reference Rate in place of that Published Rate; and

(b)

(i) aligning any provision of any Finance Document to the use of that Replacement Reference Rate;

(ii) enabling that Replacement Reference Rate to be used for the calculation of interest under this Agreement (including, without limitation, any consequential changes required to enable that Replacement Reference Rate to be used for the purposes of this Agreement);

(iii) implementing market conventions applicable to that Replacement Reference Rate;

(iv) providing for appropriate fallback (and market disruption) provisions for that Replacement Reference Rate; or

(v) adjusting the pricing to reduce or eliminate, to the extent reasonably practicable, any transfer of economic value from one Party to another as a result of the application of that Replacement Reference Rate (and if any adjustment or method for calculating any adjustment has been formally designated, nominated or recommended by the Relevant Nominating Body, the adjustment shall be determined on the basis of that designation, nomination or recommendation),

may be made with the consent of the Agent (acting on the instructions of the Majority Lenders) and the Company.

In this Clause 37.4:

"**Published Rate**" means:

(a) the Term SOFR for any Quoted Tenor; or

(b) SOFR;

"**Published Rate Replacement Event**" means, in relation to a Published Rate:

(a) the methodology, formula or other means of determining that Published Rate has, in the opinion of the Majority Lenders and the Company materially changed;

(b)

(i)

(1) the administrator of that Published Rate or its supervisor publicly announces that such administrator is insolvent; or

(2) information is published in any order, decree, notice, petition or filing, however described, of or filed with a court, tribunal, exchange, regulatory authority or similar administrative, regulatory or judicial body which reasonably confirms that the administrator of that Published Rate is insolvent,

provided that, in each case, at that time, there is no successor administrator to continue to provide that Published Rate;

(ii) the administrator of that Published Rate publicly announces that it has ceased or will cease, to provide that Published Rate permanently or indefinitely and, at that time, there is no successor administrator to continue to provide that Published Rate;

(iii) the supervisor of the administrator of that Published Rate publicly announces that such Published Rate has been or will be permanently or indefinitely discontinued; or

(iv) the administrator of that Published Rate or its supervisor announces that such Published Rate may no longer be used; or

(c) in the opinion of the Majority Lenders and the Company, that Published Rate is otherwise no longer appropriate for the purposes of calculating interest under this Agreement.

"**Quoted Tenor**" means, in relation to Term SOFR, any period for which that rate is customarily displayed on the relevant page or screen of an information service.

"**Relevant Nominated Body**" means any applicable central bank, regulator or other supervisory authority or a group of them, or any working group or committee sponsored or chaired by, or constituted at the request of, any of them or the Financial Stability Board.

"**Replacement Reference Rate**" means a reference rate which is:

(a) formally designated, nominated or recommended as the replacement for a Published Rate by:

(i) the administrator of that Published Rate (provided that the market or economic reality that such benchmark rate measures is the same as that measured by that Published Rate); or

(ii) any Relevant Nominating Body,

and if replacements have, at the relevant time, been formally designated, nominated or recommended under both paragraphs, the "Replacement Reference Rate" will be the replacement under paragraph (ii) above;

(b) in the opinion of the Majority Lenders and the Company, generally accepted in the international or any relevant domestic syndicated loan markets as the appropriate successor to a Published Rate; or

(c) in the opinion of the Majority Lenders and the Company, an appropriate successor to a Published Rate.

38. CONFIDENTIAL INFORMATION

38.1 Confidentiality

Each Finance Party agrees to keep all Confidential Information confidential and not to disclose it to anyone, save to the extent permitted by Clause 38.2 (*Disclosure of Confidential Information*) and Clause 38.3 (*Disclosure to numbering service providers*), and to ensure that all Confidential Information is protected with security measures and a degree of care that would apply to its own confidential information.

38.2 Disclosure of Confidential Information

Any Finance Party may disclose:

(a) to any of its Affiliates and Related Funds and any of its or their officers, directors, employees, professional advisers, auditors, partners and Representatives such Confidential Information as that Finance Party shall consider appropriate if any person to whom the Confidential Information is to be given pursuant to this paragraph (a) is informed in writing of its confidential nature and that some or all of such Confidential Information may be price-sensitive information except that there

shall be no such requirement to so inform if the recipient is subject to professional obligations to maintain the confidentiality of the information or is otherwise bound by requirements of confidentiality in relation to the Confidential Information;

(b) to any person:

(i) to (or through) whom it assigns or transfers (or may potentially assign or transfer) all or any of its rights and/or obligations under one or more Finance Documents or which succeeds (or which may potentially succeed) it as Agent or Security Agent and, in each case, to any of that person's Affiliates, Related Funds, Representatives and professional advisers;

(ii) with (or through) whom it enters into (or may potentially enter into), whether directly or indirectly, any sub-participation in relation to, or any other transaction under which payments are to be made or may be made by reference to, one or more Finance Documents and/or one or more Obligors and to any of that person's Affiliates, Related Funds, Representatives and professional advisers;

(iii) appointed by any Finance Party or by a person to whom paragraph (b)(i) or (ii) above applies to receive communications, notices, information or documents delivered pursuant to the Finance Documents on its behalf (including, without limitation, any person appointed under paragraph (b) of Clause 27.15 (*Relationship with the Lenders*));

(iv) who invests in or otherwise finances (or may potentially invest in or otherwise finance), directly or indirectly, any transaction referred to in paragraph (b)(i) or (b)(ii) above or any other financing source of a Finance Party who has provided financing in connection with the Facilities;

(v) to whom information is required or requested to be disclosed by any court of competent jurisdiction, any governmental, banking, taxation or other regulatory authority or similar body, the rules of any relevant stock exchange or pursuant to any applicable law or regulation;

(vi) to whom information is required to be disclosed in connection with, and for the purposes of, any litigation, arbitration, administrative or other investigations, proceedings or disputes;

(vii) to whom or for whose benefit that Finance Party charges, assigns or otherwise creates Security (or may do so) pursuant to Clause 25.8 (*Security Interests over Lenders' rights*);

(viii) who is a Party; or

(ix) with the consent of the Company;

in each case, such Confidential Information as that Finance Party shall consider appropriate if:

(1) in relation to the person to whom the Confidential Information is to be given has entered into a Confidentiality Undertaking except that there shall be no requirement for a Confidentiality Undertaking if the recipient is a professional adviser and is subject to professional

obligations to maintain the confidentiality of the Confidential Information;

(2) in relation to paragraph, the person to whom the Confidential Information is to be given has entered into a Confidentiality Undertaking or is otherwise bound by requirements of confidentiality in relation to the Confidential Information they receive and is informed that some or all of such Confidential Information may be price-sensitive information;

(3) in relation to paragraphs (b)(v), (b)(vi) and (b)(vii) above, the person to whom the Confidential Information is to be given is informed of its confidential nature and that some or all of such Confidential Information may be price-sensitive information except that there shall be no requirement to so inform if, in the opinion of that Finance Party, it is not practicable so to do in the circumstances;

(c) to any person appointed by that Finance Party or by a person to whom sub paragraph (b)(i) or (b)(ii) above applies to provide administration or settlement services in respect of one or more of the Finance Documents including without limitation, in relation to the trading of participations in respect of the Finance Documents, such Confidential Information as may be required to be disclosed to enable such service provider to provide any of the services referred to in this paragraph (c) if the service provider to whom the Confidential Information is to be given has entered into a confidentiality agreement substantially in the form of the LMA Master Confidentiality Undertaking for Use With Administration/Settlement Service Providers or such other form of confidentiality undertaking agreed between the Company and the relevant Finance Party; and

(d) to any rating agency (including its professional advisers) such Confidential Information as may be required to be disclosed to enable such rating agency to carry out its normal rating activities in relation to the Finance Documents and/or the Obligors if the rating agency to whom the Confidential Information is to be given is informed of its confidential nature and that some or all of such Confidential Information may be price-sensitive information.

38.3 **Disclosure to numbering service providers**

(a) Any Finance Party may disclose to any national or international numbering service provider appointed by that Finance Party to provide identification numbering services in respect of this Agreement, the Facilities and/or one or more Obligors the following information:

(i) names of Obligors;

(ii) country of domicile of Obligors;

(iii) place of incorporation of Obligors;

(iv) date of this Agreement;

(v) Clause 42 (*Governing law*);

(vi) the names of the Agent and the Arranger;

(vii) date of each amendment and restatement of this Agreement;

(viii) amounts of, and names of, the Facilities (and any tranches);

(ix) amount of Total Commitments;

(x) currencies of the Facilities;

(xi) type of Facilities;

(xii) ranking of Facilities;

(xiii) Termination Date for Facilities;

(xiv) changes to any of the information previously supplied pursuant to paragraphs (i) to (xiii) above; and

(xv) such other information agreed between such Finance Party and the Company,

to enable such numbering service provider to provide its usual syndicated loan numbering identification services.

(b) The Parties acknowledge and agree that each identification number assigned to this Agreement, the Facilities and/or one or more Obligors by a numbering service provider and the information associated with each such number may be disclosed to users of its services in accordance with the standard terms and conditions of that numbering service provider.

(c) The Agent shall notify the Company and the other Finance Parties of:

(i) the name of any numbering service provider appointed by the Agent in respect of this Agreement, the Facilities and/or one or more Obligors; and

(ii) the number or, as the case may be, numbers assigned to this Agreement, the Facilities and/or one or more Obligors by such numbering service provider.

38.4 **Entire agreement**

This Clause 38 constitutes the entire agreement between the Parties in relation to the obligations of the Finance Parties under the Finance Documents regarding Confidential Information and supersedes any previous agreement, whether express or implied, regarding Confidential Information.

38.5 **Inside information**

Each of the Finance Parties acknowledges that some or all of the Confidential Information is or may be price-sensitive information and that the use of such information may be regulated or prohibited by applicable legislation including securities law relating to insider dealing and market abuse and each of the Finance Parties undertakes not to use any Confidential Information for any unlawful purpose.

38.6 **Notification of disclosure**

Each of the Finance Parties agrees (to the extent permitted by law and regulation) to inform the Company of the circumstances of any disclosure by it of Confidential Information made pursuant to sub paragraph (b)(v) of Clause 38.2 (*Disclosure of Confidential Information*) except where such disclosure is made to any of the persons referred to in that paragraph during the ordinary course of its supervisory or regulatory function.

38.7 **Continuing obligations**

The obligations in this Clause 38 are continuing and, in particular, shall survive and remain binding on each Finance Party for a period of twelve months from the earlier of:

(a) The date on which all amounts payable by the Obligors under or in connection with the Finance Documents have been paid in full and all Commitments have been cancelled or otherwise cease to be available; and

(b) the date on which such Finance Party otherwise ceases to be a Finance Party.

39. **CONFIDENTIALITY OF FUNDING RATES**

39.1 **Confidentiality and disclosure**

(a) The Agent and each Obligor agree to keep each Funding Rate confidential and not to disclose it to anyone, save to the extent permitted by paragraphs (b) and (c) below.

(b) The Agent may disclose:

(i) any Funding Rate to the relevant Borrower pursuant to Clause 10.4 (*Notification of rates of interest*); and

(ii) any Funding Rate to any person appointed by it to provide administration services in respect of one or more of the Finance Documents to the extent necessary to enable such service provider to provide those services if the service provider to whom that information is to be given has entered into a confidentiality agreement substantially in the form of the LMA Master Confidentiality Undertaking for Use With Administration/Settlement Service Providers or such other form of confidentiality undertaking agreed between the Agent and the relevant Lender or Reference Bank, as the case may be.

(c) The Agent and each Obligor may disclose any Funding Rate to:

(i) any of its Affiliates and any of its or their officers, directors, employees, professional advisers, auditors, partners and Representatives if any person to whom that Funding Rate is to be given pursuant to this paragraph (i) is informed in writing of its confidential nature and that it may be price-sensitive information except that there shall be no such requirement to so inform if the recipient is subject to professional obligations to maintain the confidentiality of that Funding Rate or is otherwise bound by requirements of confidentiality in relation to it;

(ii) any person to whom information is required or requested to be disclosed by any court of competent jurisdiction or any governmental, banking, taxation or other regulatory authority or similar body, the rules of any relevant stock

exchange or pursuant to any applicable law or regulation if the person to whom that Funding Rate is to be given is informed in writing of its confidential nature and that it may be price-sensitive information except that there shall be no requirement to so inform if, in the opinion of the Agent or the relevant Obligor, as the case may be, it is not practicable to do so in the circumstances;

(iii) any person to whom information is required to be disclosed in connection with, and for the purposes of, any litigation, arbitration, administrative or other investigations, proceedings or disputes if the person to whom that Funding Rate is to be given is informed in writing of its confidential nature and that it may be price-sensitive information except that there shall be no requirement to so inform if, in the opinion of the Agent or the relevant Obligor, as the case may be, it is not practicable to do so in the circumstances; and

(iv) any person with the consent of the relevant Lender or Reference Bank, as the case may be.

39.2 **Related obligations**

(a) The Agent and each Obligor acknowledge that each Funding Rate is or may be price-sensitive information and that its use may be regulated or prohibited by applicable legislation including securities law relating to insider dealing and market abuse and the Agent and each Obligor undertake not to use any Funding Rate for any unlawful purpose.

(b) The Agent and each Obligor agree (to the extent permitted by law and regulation) to inform the relevant Lender:

(i) of the circumstances of any disclosure made pursuant to paragraph (c)(ii) of Clause 39.1 (*Confidentiality and disclosure*) except where such disclosure is made to any of the persons referred to in that paragraph during the ordinary course of its supervisory or regulatory function; and

(ii) upon becoming aware that any information has been disclosed in breach of this Clause 39.

39.3 **No Event of Default**

No Event of Default will occur under Clause 24.3 (*Other obligations*) by reason only of an Obligor's failure to comply with this Clause 39.

40. **CONTRACTUAL RECOGNITION OF BAIL-IN**

40.1 Notwithstanding any other term of any Finance Document or any other agreement, arrangement or understanding between the Parties, each Party acknowledges and accepts that any liability of any Party to any other Party under or in connection with the Finance Documents may be subject to Bail-In Action by the relevant Resolution Authority and acknowledges and accepts to be bound by the effect of:

(a) any Bail-In Action in relation to any such liability, including (without limitation):

(i) a reduction, in full or in part, in the principal amount, or outstanding amount due (including any accrued but unpaid interest) in respect of any such liability;

(ii) a conversion of all, or part of, any such liability into shares or other instruments of ownership that may be issued to, or conferred on, it; and

(iii) a cancellation of any such liability; and

(b) a variation of any term of any Finance Document to the extent necessary to give effect to any Bail-In Action in relation to any such liability.

40.2 For the purposes of this Clause 40:

"**Article 55 BRRD**" means Article 55 of Directive 2014/59/EU establishing a framework for the recovery and resolution of credit institutions and investment firms.

"**Bail-In Action**" means the exercise of any Write-down and Conversion Powers.

"**Bail-In Legislation**" means:

(a) in relation to an EEA Member Country which has implemented, or which at any time implements, Article 55 BRRD, the relevant implementing law or regulation as described in the EU Bail-In Legislation Schedule from time to time; and

(b) in relation to the United Kingdom, the UK Bail-In Legislation.

"**EEA Member Country**" means any member state of the European Union, Iceland, Liechtenstein and Norway.

"EU Bail-In Legislation Schedule" means the document described as such and published by the Loan Market Association (or any successor person) from time to time.

"Resolution Authority" means any body which has authority to exercise any Write-down and Conversion Powers.

"UK Bail-In Legislation" means Part I of the United Kingdom Banking Act 2009 and any other law or regulation applicable in the United Kingdom relating to the resolution of unsound or failing banks, investment firms or other financial institutions or their affiliates (otherwise than through liquidation, administration or other insolvency proceedings).

"Write-down and Conversion Powers" means:

(a) in relation to any Bail-In Legislation described in the EU Bail-In Legislation Schedule from time to time, the powers described as such in relation to that Bail-In Legislation in the EU Bail-In Legislation Schedule; and

(b) in relation to the UK Bail-In Legislation any powers under that UK Bail-In Legislation to cancel, transfer or dilute shares issued by a person that is a bank or investment firm or other financial institution or affiliate of a bank, investment firm or other financial institution, to cancel, reduce, modify or change the form of a liability of such a person or any contract or instrument under which that liability arises, to convert all or part of that liability into shares, securities or obligations of that person or any other person, to provide that any such contract or instrument is to have effect as if a right had been exercised under it or to suspend any obligation in respect of that liability

or any of the powers under that UK Bail-In Legislation that are related to or ancillary to any of those powers.

41. **COUNTERPARTS**

Each Finance Document may be executed in any number of counterparts, and this has the same effect as if the signatures on the counterparts were on a single copy of the Finance Document.

SECTION 12

GOVERNING LAW AND ENFORCEMENT

42. GOVERNING LAW

This Agreement and all non-contractual obligations arising in any way whatsoever out of or in connection with this Agreement shall be governed by, construed and take effect in accordance with English law.

43. ENFORCEMENT

43.1 **Jurisdiction of English courts**

(a) The courts of England have exclusive jurisdiction to decide any dispute arising out of or in connection with this Agreement (including a dispute relating to the existence, validity or termination of this Agreement or the consequences of its nullity or any non-contractual obligations arising out of or in connection with this Agreement) (a "**Dispute**").

(b) The Parties agree that the courts of England are the most appropriate and convenient courts to decide Disputes and accordingly no Party will argue to the contrary.

43.2 **Service of process**

Without prejudice to any other mode of service allowed under any relevant law, each Obligor (other than an Obligor incorporated in England and Wales):

(a) irrevocably appoints the Company at 108 Cannon Street, London EC4N 6EU at the Original Effective Date (or such other address in England and Wales as the Company may notify to the Agent in writing) as its agent for service of process in relation to any proceedings before the English courts in connection with any Finance Document (and the Company by its execution of this Agreement, accepts that appointment); and

(b) agrees that failure by an agent for service of process to notify the relevant Obligor of the process will not invalidate the proceedings concerned; and

(c) if any person appointed as an agent for service of process is unable for any reason to act as agent for service of process, the Company (on behalf of all the Obligors) must immediately (and in any event within five days of such event taking place) appoint another agent on terms acceptable to the Agent. Failing this, the Agent may appoint another agent for this purpose.

43.3 **Waiver of immunity**

Each Obligor (to the fullest extent permitted by law) irrevocably and unconditionally:

(a) agrees not to claim any immunity from proceedings brought against it by any Finance Party in relation to any Finance Document, and to ensure that no such claim is made on its behalf;

(b) waives all rights of immunity in respect of it or its assets; and

(c) consents generally in respect of such proceedings to the giving of relief or the issue of any process in connection with such proceedings.

This Agreement has been entered into on the date stated at the beginning of this Agreement and executed as a deed by each Obligor and is intended to be and is delivered by them as a deed on the date specified above.

SCHEDULE 1

The Original Parties

Part 1
The Original Obligors

The Borrower	Registration number (or equivalent, if any) and Original Jurisdiction
Orchard Therapeutics plc	11494381, England and Wales

The Original Guarantors	Registration number (or equivalent, if any) and Original Jurisdiction
Orchard Therapeutics plc	11494381, England and Wales
Orchard Therapeutics (Europe) Limited	09759506, England and Wales
Orchard Therapeutics North America	C3896310, California, USA

Part 2
The Original Lenders (as at the First Effective Date)

[***]

SCHEDULE 2

Conditions Precedent

Part 1
Conditions precedent to signing of the Agreement on the Original Effective Date

1. **OBLIGORS**

(a) A copy of the Constitutional Documents and the constitutional documents of each Original Obligor, in each case, with such amendments as the Security Agent may reasonably request.

(b) A copy of a resolution of the board or, if applicable, a committee of the board of directors of the Company and each Original Obligor:

(i) approving the terms of, and the transactions contemplated by, the Finance Documents to which it is a party and resolving that it execute, deliver and perform the Finance Documents to which it is a party;

(ii) authorising a specified person or persons to execute the Finance Documents to which it is a party on its behalf; and

(iii) authorising a specified person or persons, on its behalf, to sign and/or despatch all documents and notices (including, if relevant, any Utilisation Request and Selection Notice) to be signed and/or despatched by it under or in connection with the Finance Documents to which it is a party.

(c) If applicable, a copy of a resolution of the board of directors of the relevant company, establishing the committee referred to in paragraph (b) above.

(d) A specimen of the signature of each person authorised by the resolution referred to in paragraph (b) above in relation to the Finance Documents and related documents.

(e) If required by applicable law, a copy of a resolution signed by all the holders of the issued shares in each Original Obligor (other than the Company), approving the terms of, and the transactions contemplated by, the Finance Documents to which the Original Obligor is a party.

(f) If applicable, a copy of a resolution of the board of directors of each corporate shareholder of each Original Obligor (other than the Company) approving the terms of the resolution referred to in paragraph (e) above.

(g) A certificate of the Company (signed by a director or officer) confirming that borrowing or guaranteeing or securing, as appropriate, the Total Commitments would not cause any borrowing, guarantee, security or similar limit binding on it or Orchard Therapeutics (Europe) Limited to be exceeded.

(h) A certificate of the Orchard Therapeutics North America (signed by a director or officer) confirming that borrowing or guaranteeing or securing, as appropriate, the Total Commitments would not cause any borrowing, guarantee, security or similar limit binding on it to be exceeded.

(i) A certificate of an authorised signatory of the Company certifying that each copy document relating to it and Orchard Therapeutics (Europe) Limited specified in this Part 1 of Schedule 2 is correct, complete and in full force and effect and has not been amended or superseded as at a date no earlier than the date of this Agreement.

(j) A certificate of an authorised signatory of Orchard Therapeutics North America certifying that each copy document relating to it specified in this Part 1 of Schedule 2 is correct, complete and in full force and effect and has not been amended or superseded as at a date no earlier than the date of this Agreement.

(k) With respect to each US Obligor, a long-form certificate of good standing and certified charter documents from the Secretary of State of such Person's state of organisation).

2. **FINANCE DOCUMENTS**

(a) This Agreement executed by members of the Group party to this Agreement.

(b) The Fee Letters executed by the Company.

(c) At least two originals of each of the following Transaction Security Documents executed by the Original Obligor specified below opposite the relevant Transaction Security Document:

Name of Original Obligor	**Transaction Security Document**	**Governing law of document**
The Company	Debenture	English law
Orchard Therapeutics (Europe) Limited	Debenture	English law
Orchard Therapeutics (Europe) Limited	Pledge Agreement	New York law
Orchard Therapeutics North America	Security Agreement	New York law

(d) A copy of all notices required to be sent under the Transaction Security Documents duly acknowledged by the addressees.

(e) Originals of all share certificates, transfers and stock transfer forms (all stock transfer forms to be executed by two directors or a director and the secretary of the company that owns the relevant shares but with the sections relating to the consideration and the transferee left blank) or equivalent, duly executed by the relevant Obligor in relation to the assets subject to or expressed to be subject to the Transaction Security and other documents of title to be provided under the Transaction Security Documents.

(f) In respect of each company incorporated in the United Kingdom whose shares are the subject of the Transaction Security (a "**Charged Company**"), either:

(i) a certificate of an authorised signatory of the Company certifying that:

(1) each member of the Group has complied within the relevant timeframe with any notice it has received pursuant to Part 21A of the Companies Act 2006 from that Charged Company; and

(2) no "warning notice" or "restrictions notice" (in each case as defined in Schedule 1B of the Companies Act 2006) has been issued in respect of those shares,

together with a copy of the "PSC register" (within the meaning of section 790C(10) of the Companies Act 2006) of that Charged Company which, in the case of a Charged Company that is a member of the Group, is certified by an authorised signatory of the Company to be correct, complete and not amended or superseded as at a date no earlier than the date of this Agreement; or

(ii) a certificate of an authorised signatory of the Company certifying that such Charged Company is not required to comply with Part 21A of the Companies Act 2006.

(g) Any document or information required to be delivered to the Agent or the Security Agent on or prior to the Closing Date pursuant to the terms of any Transaction Security Document and not otherwise specifically referred to in this Schedule.

3. **LEGAL OPINIONS**

The following legal opinions, each addressed to the Agent, the Security Agent and the Original Lenders and capable of being relied upon by any persons who become Lenders pursuant to the primary syndication of the Facilities:

(a) a legal opinion of Hogan Lovells International LLP, legal advisers to the Agent and the Arranger as to English law substantially in the form distributed to the Original Lenders prior to signing this Agreement;

(b) a legal opinion of Ashurst LLP, legal advisers to the US Obligor as to California law substantially in the form distributed to the Original Lenders prior to signing this Agreement; and

(c) a legal opinion of Ashurst LLP, legal advisers to the US Obligor as to New York law substantially in the form distributed to the Original Lenders prior to signing this Agreement,

each substantially in the form distributed to the Original Lenders prior to signing this Agreement.

4. **OTHER DOCUMENTS AND EVIDENCE**

(a) Evidence that any process agent referred to in Clause 43.2 (*Service of process*), if not an Original Obligor, has accepted its appointment.

(b) The Investment Policy.

(c) The Group Structure Chart.

(d) The Base Case Model.

(e) A copy, certified by an authorised signatory of the Company to be a true copy, of the Original Financial Statements of each Obligor.

(f) A copy of any other Authorisation or other document, opinion or assurance which the Agent considers to be necessary (if it has notified the Company accordingly) in connection with the entry into and performance of the transactions contemplated by any Finance Document or for the validity and enforceability of any Finance Document.

(g) Any information and evidence in respect of any Obligor required by any Finance Party to enable it to be satisfied with the results of all "know your customer" or other checks which it is required to carry out in relation to such person.

(h) Evidence that the fees, costs and expenses then due from the Company pursuant to Clause 13 (*Fees*), Clause 14.6 (*Stamp taxes*) and Clause 18 (*Costs and expenses)* have been paid or will be paid by the first Utilisation Date.

(i) Lien searches customary in the jurisdiction of formation of such Original Obligor.

(j) Financing Statements (or local law equivalents) required pursuant to any Financing Document.

Part 2
Conditions precedent required to be delivered by an Additional Obligor

1. An Accession Deed executed by the Additional Obligor and the Company.

2. A copy of the constitutional documents of the Additional Obligor, with such amendments as the Agent may reasonably require.

3. A copy of a resolution of the board of directors of the Additional Obligor:

   (a) approving the terms of, and the transactions contemplated by, the Accession Deed and the Finance Documents and resolving that it execute, deliver and perform the Accession Deed and any other Finance Document to which it is party;

   (b) authorising a specified person or persons to execute the Accession Deed and other Finance Documents on its behalf;

   (c) authorising a specified person or persons, on its behalf, to sign and/or despatch all other documents and notices to be signed and/or despatched by it under or in connection with the Finance Documents to which it is a party; and

   (d) authorising the Company to act as its agent in connection with the Finance Documents.

4. A specimen of the signature of each person authorised by the resolution referred to in paragraph 3 above.

5. If required by applicable law, a copy of a special resolution signed by all the holders of the issued shares of the Additional Guarantor, approving the terms of, and the transactions contemplated by, the Finance Documents to which the Additional Guarantor is a party.

6. If applicable, a copy of a resolution of the board of directors of each corporate shareholder of each Additional Guarantor approving the terms of the resolution referred to in paragraph 5 above.

7. A certificate of the Additional Obligor (signed by a director or officer) confirming that: (1) borrowing or guaranteeing or securing, as appropriate, the Total Commitments would not cause any borrowing, guarantee, security or similar limit binding on it to be exceeded; and (2) the Additional Obligor has positive net assets.

8. A certificate of an authorised signatory of the Additional Obligor certifying that each copy document listed in this Part 2 of Schedule 2 is correct, complete and in full force and effect and has not been amended or superseded as at a date no earlier than the date of the Accession Deed.

9. A copy of any other Authorisation or other document, opinion or assurance which the Agent considers to be necessary or desirable in connection with the entry into and performance of the transactions contemplated by the Accession Deed or for the validity and enforceability of any Finance Document.

10. If available, the latest audited financial statements of the Additional Obligor.

11. The following legal opinions, each addressed to the Agent, the Security Agent and the Lenders:

(a) A legal opinion of Hogan Lovells International LLP as advisers to the Agent in England, as to English law in the form distributed to the Lenders prior to signing the Accession Deed.

(b) If the Additional Obligor is incorporated in or has its "centre of main interest" or "establishment" (as referred to in Clause 20.27 (*Centre of main interests and establishments*)) in a jurisdiction other than England and Wales or is executing a Finance Document which is governed by a law other than English law, a legal opinion of the legal advisers to the Agent in the jurisdiction of its incorporation, "centre of main interest" or "establishment" (as applicable) or, as the case may be, the jurisdiction of the governing law of that Finance Document (the "**Applicable Jurisdiction**") as to the law of the Applicable Jurisdiction and in the form distributed to the Lenders prior to signing the Accession Deed and, in the case of an Additional Obligor that will be a US Obligor, the legal advisers to the Company or to the Additional Obligor will also provide customary opinions (including as to creation and perfection of security interests) as to New York law, Delaware law (or such other state, territory or district as shall be the jurisdiction of organisation of that US Obligor or whose law shall govern with respect to the perfection of security interests) and the federal law of the United States. The legal advisers to the Company or to the Additional Obligor will also provide customary opinions with respect to security interests granted by non-US Obligors covering interests in US companies or US property.

(c) If an Obligor or Additional Obligor (as the case may be) grants security over the shares it owns in a Subsidiary where that Subsidiary is incorporated in a different jurisdiction from the jurisdiction of that Obligor, legal opinions of the legal advisers to the Agent:

(i) in the Applicable Jurisdiction for the relevant Transaction Security Document; and

(ii) in the jurisdiction where the relevant Obligor or Additional Obligor is incorporated, or has its centre of main interests or "establishment" (as applicable).

12. If the proposed Additional Obligor is incorporated in a jurisdiction other than England and Wales, evidence that the process agent specified in Clause 43.2 (*Service of process*), if not an Obligor, has accepted its appointment in relation to the proposed Additional Obligor.

13.

(a) The Transaction Security Documents or other security documents which subject to the Agreed Security Principles are required by the Agent to be executed by the proposed Additional Obligor.

(b) Such evidence concerning the PSC register (within the meaning of S790C(10) of the Act) of any company incorporated in the United Kingdom whose shares are to be charged by an Additional Obligor as the Agent may reasonably request.

14. Any notices or documents (including title deeds) required to be given or executed under the terms of those security documents referred to in paragraph 13 above.

15. Share certificates and stock transfer forms executed in blank (as described in paragraph 2(e) of Part 1 of this Schedule) as required by any security document.

16.

(a) In relation to Additional Obligors incorporated in England and Wales or Scotland, evidence that members of the Group incorporated in England and Wales or Scotland have done all that is necessary (including, without limitation, by re-registering as a private company) to ensure that the relevant Additional Obligor can enter into the Finance Documents and perform its obligations under the Finance Documents without breach of any applicable financial assistance or capital maintenance laws. Such evidence shall include copies of board and special resolutions for each relevant Additional Obligor and copies of the registers of directors and shareholders of each relevant Additional Obligor.

(b) If the Additional Obligor is not incorporated in England and Wales or Scotland, such documentary evidence as legal counsel to the Agent may require, that such Additional Obligor:

(i) has complied with any law in its jurisdiction relating to financial assistance or analogous process; and

(ii) is not an overseas company which has registered an establishment in the UK under the Overseas Companies Regulations 2009 (SI 2009/1801), or, if that Additional Obligor has so registered a UK establishment: (1) giving the full name and registered number of such UK establishment; (2) attaching a certified copy of that company's own internal register of charges; and (3) confirming that the Additional Obligor has not created any charges (whether registrable or not) which have not been registered on that register of charges for any reason.

17. Evidence that all necessary or desirable Authorisations from any government authority or other regulatory body in connection with the entry into and performance of the transactions contemplated by the Accession Deed, any Finance Document or Transaction Document to which the Additional Obligor is party or for the validity or enforceability of any of those documents have been obtained and are in full force and effect, together with certified copies of those obtained.

18. A certificate of the Company confirming that no Default is continuing or would occur as a result of the Additional Obligor executing the Accession Deed or the Finance Documents or the Finance Documents to which it is party.

19. Such other information or documents that the Agent may reasonably require, including any information and evidence in respect of the Additional Obligor required by any Finance Party to enable it to be satisfied with the results of all "know your customer" or other checks which it is required to carry out in relation to such Obligor.

20. A copy of the register listing the directors of the Additional Obligor.

21. If the Additional Obligor is incorporated in a state of the United States or the District of Columbia each US Obligor also will be required to deliver a certificate of good standing and certified charter documents from the Secretary of State of the State of Delaware (or other state of organisation).

22. Lien searches customary in the jurisdiction of formation of such Additional Obligor.

23. Financing Statements (or local law equivalents) required pursuant to any Financing Document.

SCHEDULE 3

Requests

Part 1
Utilisation Request

From: [Borrower]/[Company]

To: [Agent]

Dated:

Dear Sirs

[COMPANY] – SENIOR FACILITIES AGREEMENT DATED [*] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This is a Utilisation Request. Terms defined in the Facilities Agreement have the same meaning in this Utilisation Request unless given a different meaning in this Utilisation Request.

2. We wish to borrow a Loan on the following terms:

(a)	Borrower:	[***]
(b)	Proposed Utilisation Date:	[***] (or, if that is not a Business Day, the next Business Day)
(c)	Facility to be utilised:	[Facility A1]/[Facility A2]/[Facility B]/[Facility C]
(d)	Currency of Loan:	US Dollars
(e)	Amount:	[***] or, if less, the Available Facility
(f)	Interest Period:	[***]

3. We confirm that each condition specified in Clause 4.2 (*Further conditions precedent*) of the Facilities Agreement is satisfied on the date of this Utilisation Request.

4. The proceeds of this Loan should be credited to [account].

5. This Utilisation Request is irrevocable.

Yours faithfully

……

authorised signatory for

[the Company on behalf of [insert name of relevant Borrower]/[insert name of Borrower]

Part 2
Selection Notice

From: [Borrower]/[Company]

To: [Agent]

Dated:

Dear Sirs

[COMPANY] - [*] SENIOR FACILITIES AGREEMENT DATED [***] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This is a Selection Notice. Terms defined in the Facilities Agreement have the same meaning in this Selection Notice unless given a different meaning in this Selection Notice.

2. We refer to the following [Facility A1 Loan / Facility A2 Loan / Facility B Loan / Facility C Loan].

3. We request that the next Interest Period for the above Loan[s] is [***].

4. This Selection Notice is irrevocable.

Yours faithfully,

.....

authorised signatory for
[the Company on behalf of]/[*insert name of Relevant Borrower*]

SCHEDULE 4

Form of Transfer Certificate

To: [***] as Agent and [***] as Security Agent

From: [The Existing Lender] (the "**Existing Lender**") and [The New Lender] (the "**New Lender**")

Dated:

[COMPANY] – SENIOR FACILITIES AGREEMENT DATED [*] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This agreement (the "**Agreement**") shall take effect as a Transfer Certificate for the purpose of the Facilities Agreement. Terms defined in the Facilities Agreement have the same meaning in this Agreement unless given a different meaning in this Agreement.

2. We refer to Clause 25.5 (*Procedure for transfer*) of the Facilities Agreement:

   (a) The Existing Lender and the New Lender agree to the Existing Lender transferring to the New Lender by novation and in accordance with Clause 25.5 (*Procedure for transfer*) of the Facilities Agreement all of the Existing Lender's rights and obligations under the Facilities Agreement, the other Finance Documents and in respect of the Transaction Security which relate to that portion of the Existing Lender's Commitment(s) and participations in Utilisations under the Facilities Agreement as specified in the Schedule [OR] [*** Each Existing Lender listed in Part 1 of the Schedule transfers by novation to each New Lender listed in Part 2 of the Schedule that portion of the outstanding Utilisations and Commitments in accordance with Clause 25.5 (*Procedure for transfer*), such that:

      (i) each New Lender will become a Lender under the Agreement with the respective Commitment and portion of outstanding Utilisations set out opposite its name in Part 3 of the Schedule; and

      (ii) each Existing Lender's Commitment and portion of outstanding Utilisations will be reduced to the amounts set out opposite its name in Part 3 of the Schedule. ***]

   (b) The proposed Transfer Date is [***].

   (c) The Facility Office and address, fax number and attention details for notices of the New Lender for the purposes of Clause 33.2 (*Addresses*) of the Facilities Agreement are set out in the Schedule.

3. [*** The/Each ***] New Lender expressly acknowledges the limitations on the Existing Lender['s][s'] obligations set out in paragraph (c) of Clause 25.4 (*Limitation of responsibility of Existing Lenders*) of the Facilities Agreement.

4. The New Lender confirms, for the benefit of the Agent and without liability to any Obligor, that it is:

   (a) [a Qualifying Lender (other than a Treaty Lender);]

   (b) [a Treaty Lender;]

   (c) [not a Qualifying Lender].

5. [*** The/Each New Lender confirms that the person beneficially entitled to interest payable to that Lender in respect of an advance under a Finance Document is either:

   (a) a company resident in the United Kingdom for United Kingdom tax purposes; or

   (b) a partnership each member of which is:

      (i) a company so resident in the United Kingdom; or

      (ii) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and brings into account in computing its chargeable profits (within the meaning of section 19 of the CTA) the whole of any share of interest payable in respect of that advance that falls to it by reason of Part 17 of the CTA; or

   (c) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account interest payable in respect of that advance in computing the chargeable profits (within the meaning of section 19 of the CTA) of that company.

6. [The New Lender confirms that it holds a passport under the HMRC DT Treaty Passport scheme (reference number [ ]) and is tax resident in [insert jurisdiction of tax residence], so that interest payable to it by borrowers is generally subject to full exemption from UK withholding tax requests that the Company notify

   (a) each Borrower which is a Party as a Borrower as at the Transfer Date ; and

   (b) each Additional Borrower which becomes an Additional Borrower after the Transfer Date,

   that it wishes that scheme to apply to the Facilities Agreement.]

7. This Agreement may be executed in any number of counterparts and this has the same effect as if the signatures on the counterparts were on a single copy of this Agreement.

8. For the purpose of Clause 33.7 (*Use of websites*) the New Lender is a [*** Website Lender ***] [*** Paper Form Lender ***]. ***] OR [*** each New Lender specifies in Part 4 of the Schedule opposite its name whether it is a Website Lender or a Paper Form Lender. ***]

9. This Agreement and all non-contractual obligations arising in any way whatsoever out of or in connection with this Agreement shall be governed by, construed and take effect in accordance with English law.

10. This Agreement has been entered into on the date stated at the beginning of this Agreement.

Note: **The execution of this Transfer Certificate may not transfer a proportionate share of the Existing Lender's interest in the Transaction Security in all jurisdictions. It is the responsibility of the New Lender to ascertain whether any other documents or other formalities are required to perfect a transfer of such a share in the Existing Lender's Transaction Security in any jurisdiction and, if so, to arrange for execution of those documents and completion of those formalities.**

The Schedule

Commitment/rights and obligations to be transferred

[*insert relevant details*]

[*Facility Office address, fax number and attention details for notices and account details for payments*,]

[Existing Lender]	[New Lender]
By:	By:

This Agreement is accepted as a Transfer Certificate for the purposes of the Facilities Agreement by the Agent and the Security Agent and the Transfer Date is confirmed as [***].

[Agent]

By:

[Security Agent]

By:

SCHEDULE 5

Form of Assignment Agreement

To: [***] as Agent, [***] ad Security Agent and [***] as Company, for and on behalf of each Obligor.

From: [the *Existing Lender*] (the "**Existing Lender**") and [the *New Lender*] (the "**New Lender**")

Dated: [***]

[COMPANY] - [*] SENIOR FACILITIES AGREEMENT DATED [***] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This is an Assignment Agreement. This agreement (the "**Agreement**") shall take effect as an Assignment Agreement for the purposes of the Facilities Agreement. Terms defined in the Facilities Agreement have the same meaning in this Agreement unless given a different meaning in this Agreement.

2. We refer to Clause 25.6 (*Procedure for assignment*) of the Facilities Agreement.

   (a) The Existing Lender assigns absolutely to the New Lender all the rights of the Existing Lender under the Facilities Agreement, the other Finance Documents and in respect of the Transaction Security which correspond to that portion of the Existing Lender's Commitment(s) and participations in Utilisations under the Facilities Agreement as specified in the Schedule;

   (b) The Existing Lender is released from all the obligations of the Existing Lender which correspond to that portion of the Existing Lender's Commitment(s) and participations in Utilisations under the Facilities Agreement specified in the Schedule.

   (c) The New Lender becomes a Party as a Lender and is bound by obligations equivalent to those from which the Existing Lender is released under paragraph (b) above.

3. The proposed Transfer Date is [***]

4. On the Transfer Date the New Lender becomes Party to the relevant Finance Documents as a Lender.

5. The Facility office and address, fax number and attention details for notices of the New Lender for the purposes of Clause 33.2 (*Addresses*) of the Facilities Agreement are set out in the Schedule.

6. The New Lender expressly acknowledges the limitations on the Existing Lender's obligations set out in paragraph (c) of Clause 25.4 (*Limitation of responsibility of Existing Lenders*) of the Facilities Agreement.

7. The New Lender confirms, for the benefit of the Agent and without liability to any Obligor, that it is:

   (a) [a Qualifying Lender (other than a Treaty Lender);]

   (b) [a Treaty Lender;]

   (c) [not a Qualifying Lender].

8. [*** The New Lender confirms that the person beneficially entitled to interest payable to that Lender in respect of an advance under a Finance Document is either:

   (a) a company resident in the United Kingdom for United Kingdom tax purposes;

   (b) a partnership each member of which is:

      (i) a company so resident in the United Kingdom; or

      (ii) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and brings into account in computing its chargeable profits (within the meaning of section 19 of the CTA) the whole of any share of interest payable in respect of that advance that falls to it by reason of Part 17 of the CTA; or

   (c) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account interest payable in respect of that advance in computing the chargeable profits (within the meaning of section 19 of the CTA) of that company.

9. [The New Lender confirms that it holds a passport under the HMRC DT Treaty Passport scheme (reference number [ ]) and is tax resident in [insert jurisdiction of tax residence], so that interest payable to it by borrowers is generally subject to full exemption from UK withholding tax requests that the Company notify:

   (a) each Borrower which is a Party as a Borrower as at the Transfer Date; and

   (b) each Additional Borrower which becomes an Additional Borrower after the Transfer Date

   the Borrower that it wishes that scheme to apply to the Facilities Agreement.]

10. This Agreement acts as notice to the Agent (on behalf of each Finance Party) and upon delivery in accordance with Clause 25.7 (*Copy of Transfer Certificate, Assignment Agreement or Increase Confirmation to Company*) to the Company (on behalf of each Obligor) of the assignment referred to in this Assignment Agreement.

11. This Agreement may be executed in any number of counterparts and this has the same effect as if the signatures on the counterparts were on a single copy of this Assignment Agreement.

12. For the purpose of Clause 33.7 (*Use of websites*) the New Lender is a [*** Website Lender ***] [*** Paper Form Lender ***]

13. This Agreement and all non-contractual obligations arising in any way whatsoever out of or in connection with this Assignment Agreement shall be governed by, construed and take effect in accordance with English law.

14. This Agreement has been entered into on the date stated at the beginning of this Agreement.

Note: **The execution of this Assignment Agreement may not transfer a proportionate share of the Existing Lender's interest in the Transaction Security in all jurisdictions. It is the responsibility of the New Lender to ascertain whether any other documents or other formalities are required**

to perfect a transfer of such a share in the Existing Lender's Transaction Security in any jurisdiction and, if so, to arrange for execution of those documents and completion of those formalities.

THE SCHEDULE

Commitment/rights and obligations to be transferred by

assignment, release and accession

[*** insert relevant details ***]

[*** Facility office address, fax number and attention details for notices and account details for payments ***]

[*** Existing Lender ***]	[*** New Lender ***]
By:	By:

This Agreement is accepted as an Assignment Agreement for the purposes of the Facilities Agreement by the Agent and the Security Agent and the Transfer Date is confirmed as [***].

[*** Signature of this Agreement by confirmation by the Agent of receipt of notice of the assignment referred to in this Agreement, which notice the Agent receives on behalf of each Finance Party. ***]

[*** Agent ***]

By:

[*** Security Agent ***]

By:

SCHEDULE 6

Form of Accession Deed

To: [***] as Agent

From: [Subsidiary] and [Company]

Dated:

Dear Sirs

[COMPANY] – SENIOR FACILITIES AGREEMENT DATED [*] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This deed (the "**Accession Deed**") shall take effect as an Accession Deed for the purposes of the Facilities Agreement. Terms defined in the Facilities Agreement have the same meaning in paragraphs 1-4 of this Accession Deed unless given a different meaning in this Accession Deed.

2. [Subsidiary] agrees to become an Additional [Borrower]/[Guarantor] and to be bound by the terms of the Facilities Agreement and the other Finance Documents as an Additional [Borrower]/[Guarantor] pursuant to [Clause 26.2 (*Additional Borrowers*)]/[Clause 26.2 (*Additional Guarantors*)] of the Facilities Agreement. [Subsidiary] is a company duly incorporated under the laws of [name of relevant jurisdiction] and is a limited liability company with registered number [***].

3. [The Company confirms that no Default is continuing or would occur as a result of [Subsidiary] becoming an Additional Borrower.]

4. [Subsidiary's] administrative details for the purposes of the Facilities Agreement are as follows:

   Address:

   Fax No.:

   Attention:

   the "**Relevant Documents**".

5. This Accession Deed [and all non-contractual obligations arising in any way whatsoever out of or in connection with this Accession Deed] shall be governed by, construed and take effect in accordance with English law.

THIS ACCESSION DEED has been signed on behalf of the Company and executed as a deed by [Subsidiary] and is delivered on the date stated above.

[**SUBSIDIARY**]

[Executed as a Deed)

by: [**Subsidiary**])

Director

Director/Secretary

OR

[Executed as a Deed)

by: [**Subsidiary**])

Signature of Director: _____

Name of Director: _____

in the presence of:

Signature of witness:

Name of witness: _____

Address of witness: _____

_____

_____

_____

_____

_____

Occupation of witness: _____

THE COMPANY

[Company]

By:

SCHEDULE 7

Form of Resignation Letter

To: [ ] as Agent

From: [resigning Obligor] and [Company]

Dated:

Dear Sirs

[COMPANY] – [ ] SENIOR FACILITIES AGREEMENT DATED [ ] (THE "FACILITIES AGREEMENT")

1. We refer to the Facilities Agreement. This is a Resignation Letter. Terms defined in the Facilities Agreement have the same meaning in this Resignation Letter unless given a different meaning in this Resignation Letter.

2. Pursuant to [Clause 26.3 (*Resignation of a Borrower*)]/[Clause 26.5 (*Resignation of a Guarantor*)] of the Facilities Agreement, we request that resigning Obligor be released from its obligations as a [Borrower]/[Guarantor] under the Facilities Agreement and the Finance Documents.

3. We confirm that:

   (a) no Default is continuing or would result from the acceptance of this request; and

   (b) this request is given in relation to a Third Party Disposal of [resigning Obligor];

   (c) the Disposal Proceeds have been or will be applied in accordance with Clause 8.2 (*Disposal, Insurance and Acquisition Proceeds*) of the Facilities Agreement;

   (d) [ ].

4. This Resignation Letter and any non-contractual obligations arising out of or in connection with it are governed by English law.

[Company]	[resigning Obligor]
By:	By:

SCHEDULE 8

Form of Compliance Certificate

To: [***] as Agent

From: [Company]

Dated:

Dear Sirs

[COMPANY] - SENIOR FACILITIES AGREEMENT DATED [*] (THE "FACILITIES AGREEMENT")**

1. We refer to the Facilities Agreement. This is a Compliance Certificate. Terms defined in the Facilities Agreement have the same meaning when used in this Compliance Certificate unless given a different meaning in this Compliance Certificate.

2. We confirm that:

   [Insert details of covenants to be certified] and the aggregate amount of cash and cash equivalents held by the Group as of the date hereof is $[____] and the aggregate amount of Group Unrestricted Cash as of the date hereof is $[____].

   [Net Revenue for the trailing twelve month period ended as of the date hereof, was $[____], as evidenced by the Financial Statements attached hereto.]

3. We confirm that no Default is continuing.

Signed: ……..	……
Director/Officer Of [Company]	Director/Officer Of [Company]

SCHEDULE 9

Timetables

Loans

	Loans in dollars
Delivery of a duly completed initial Utilisation Request (Clause 5.1 (*Delivery of a Utilisation Request*)) or a Selection Notice (Clause 11.1 (*Selection of Interest Periods and Terms*))	U-2 9.30 am
Delivery of a duly completed Utilisation Request (other than the initial Utilisation Request) (Clause 5.1 (*Delivery of a Utilisation Request*))	U-10 9.30 am
Agent determines (in relation to a Utilisation) the amount of the Loan, if required under Clause 5.4 (*Lenders' participation*) and notifies the Lenders of the Loan in accordance with Clause 5.4 (*Lenders' participation*)	U-1 Noon
Reference Rate is fixed	Quotation Day

"**U**" = date of utilisation or, if applicable, in the case of a Loan that has already been borrowed, the first day of the relevant Interest Period for that Loan.

"**U-X**" = X Business Days prior to date of utilisation

SCHEDULE 10

Form of Increase Confirmation

To: [ ] as Agent, [ ] as Security Agent and [ ] as Company, for and on behalf of each Obligor

From: [the Increase Lender] (the "Increase Lender")

Dated:

[COMPANY] - [ ] SENIOR FACILITIES AGREEMENT DATED [ ] (THE "FACILITIES AGREEMENT")

1. We refer to the Facilities Agreement. This agreement (the "**Agreement**") shall take effect as an Increase Confirmation for the purpose of the Facilities Agreement. Terms defined in the Facilities Agreement have the same meaning in this Agreement unless given a different meaning in this Agreement.

2. We refer to Clause 2.2 (*Increase*) of the Facilities Agreement.

3. The Increase Lender agrees to assume and will assume all of the obligations corresponding to the Commitment specified in the Schedule (the "**Relevant Commitment(s)**") as if it had been an Original Lender under the Facilities Agreement in respect of the Relevant Commitment(s).

4. The proposed date on which the increase in relation to the Increase Lender and the Relevant Commitment(s) is to take effect (the "**Increase Date**") is [***].

5. On the Increase Date, the Increase Lender become party to the relevant Finance Documents as a Lender.

6. The Facility Office and address, fax number and attention details for notices to the Increase Lender for the purposes of Clause 33.2 (*Addresses*) of the Facilities Agreement are set out in the Schedule.

7. The Increase Lender expressly acknowledges the limitations on the Lenders' obligations referred to in paragraph (k) of Clause 2.2 (*Increase*) of the Facilities Agreement .

8. The Increase Lender confirms, for the benefit of the Agent and without liability to any Obligor, that it is:

   (a) [a Qualifying Lender (other than a Treaty Lender);]

   (b) [a Treaty Lender;]

   (c) [not a Qualifying Lender].

9. [The Increase Lender confirms that the person beneficially entitled to interest payable to that Lender in respect of an advance under a Finance Document is either:

   (a) a company resident in the United Kingdom for United Kingdom tax purposes;

   (b) a partnership each member of which is:

      (i) a company so resident in the United Kingdom; or

      (ii) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings

into account in computing its chargeable profits (within the meaning of section 19 of the CTA) the whole of any share of interest payable in respect of that advance that falls to it by reason of Part 17 of the CTA; or

(c) a company not so resident in the United Kingdom which carries on a trade in the United Kingdom through a permanent establishment and which brings into account interest payable in respect of that advance in computing the chargeable profits (within the meaning of section 19 of the CTA) of that company.]

10. [The Increase Lender confirms that it holds a passport under the HMRC DT Treaty Passport scheme (reference number [ ]) and is tax resident in [insert jurisdiction of tax residence], so that interest payable to it by borrowers is generally subject to full exemption from UK withholding tax and requests that the Company notify:

(a) each Borrower which is a Party as a Borrower as at the Increase Date; and

(b) each Additional Borrower which becomes an Additional Borrower after the Increase Date,

that it wishes the scheme to apply to the Facilities Agreement.]

11. This Agreement may be executed in any number of counterparts and this has the same effect as if the signatures on the counterparts were on a single copy of this Agreement.

12. This Agreement [and any non-contractual obligations arising out of or in connection with it] [is/are] governed by English law.

13. This Agreement has been entered into on the date stated at the beginning of this Agreement.

Note: The execution of this Increase Confirmation may not be sufficient for the Increase Lender to obtain the benefit of the Transaction Security in all jurisdictions. It is the responsibility of the Increase Lender to ascertain whether any other documents or other formalities are required to obtain the benefit of the Transaction Security in any jurisdiction and, if so, to arrange for execution of those documents and completion of those formalities.

THE SCHEDULE

Relevant Commitment/rights and obligations to be assumed by the Increase Lender

[insert relevant details]

[Facility office address, fax number and attention details for notices and account details for payments]

[Increase Lender]

By:

This Agreement is accepted as an Increase Confirmation for the purposes of the Facilities Agreement by the Agent and the Increase Date is confirmed as [ ].

Agent

By:

SCHEDULE 11

Agreed Security Principles

1. **DEFINITIONS**

In this Schedule:

"**Secured Liabilities**" means all present and future obligations and liabilities (whether actual or contingent and whether owed jointly or severally or in any other capacity whatsoever) of each Obligor to all or any of the Secured Parties under each or any of the Finance Documents together with:

(a) all costs, charges and expenses incurred by any Secured Party in connection with the protection, preservation or enforcement of its rights under any Finance Document; and

(b) all moneys, obligations and liabilities due, owing or incurred in respect of any variations or increases in the amount or composition of the facilities provided under any Finance Document or the obligations and liabilities imposed under such documents.

"cost" includes, but is not limited to, tax costs, registration taxes payable on the creation or enforcement or for the continuance of any Security, stamp duties, out-of-pocket expenses, and other fees and expenses incurred (or which would be incurred) by the relevant member of the Group or any of its direct or indirect Holding Companies, Subsidiaries or Affiliates directly as a consequence of the provision of relevant Security or guarantees.

2. **SCOPE OF THE AGREED SECURITY PRINCIPLES**

Guarantees and Security to be provided pursuant to this Agreement will be given in accordance with the Agreed Security Principles set out in this Schedule.

3. **CONSIDERATIONS**

3.1 Subject to paragraph 3.2 below, Security and/or guarantees shall not be created or perfected to the fullest extent possible if it would result in:

(a) any breach of corporate benefit, financial assistance, fraudulent preference, thin capitalisation rules or any other general statutory laws or regulations (or analogous restrictions) of any applicable jurisdiction;

(b) the officers of a member of the Group contravening their fiduciary duties or any legal prohibition and/or result in them incurring civil or criminal liability; or

(c) costs that, in the opinion of the Agent (acting reasonably), will be disproportionate to the benefit to be obtained by the Secured Parties,

provided that the relevant member of the Group will use its best endeavours (including the payment of reasonable fees, cost and expenses if necessary) to overcome any such obstacle, including ensuring that each Obligor has positive net assets when it executes the Transaction Security and the guarantees contained in the Finance Documents.

3.2 The considerations in paragraph 3.1(c) shall not apply to the Security and guarantees required from the Original Obligors, which those Obligors have agreed to provide irrespective of cost or materiality.

4. **Obligations to be secured**

4.1 Subject to paragraph 4.3 below, the obligations to be secured are the Secured Liabilities and, for ease of reference, this definition (as well as the definition of Secured Parties from this Agreement) should to the extent legally possible be incorporated in all material respects into each Transaction Security Document.

4.2 Each guarantee will be an upstream, cross-stream and downstream guarantee.

4.3 If it is necessary to do so, the Secured Liabilities will be limited:

(a) to avoid any breach of corporate benefit, financial assistance, fraudulent preference or thin capitalisation rules or other general statutory laws or regulations (or analogous restrictions) of any applicable jurisdiction; and

(b) to avoid any significant risk to officers of the relevant member of the Group of contravention of their fiduciary duties and/or civil or criminal liability.

4.4 The extent of the Secured Liabilities may be limited, in accordance with market practice in the relevant jurisdiction, to minimise stamp duty, notarisation, registration or other applicable fees, taxes and duties where the Majority Lenders have agreed that, in their opinion, the benefit of increasing the amount recoverable under the relevant Security or guarantee is, disproportionate to the level of such additional fee, tax or duty. Any financial limitation on the amount recoverable under the Secured Liabilities shall take into consideration the underlying value of the assets being provided as Security.

4.5 To the extent legally possible, all guarantees and Security shall be given in favour of the Security Agent and not the Secured Parties individually. "Parallel debt" provisions will be used where necessary in a particular jurisdiction.

4.6 To the greatest extent possible, no action should be required to be taken in relation to any guarantees and/or Security when any Secured Party transfers any of its interests to a new participant.

5. **The Security**

5.1 The Security is to be granted in favour of the Security Agent on behalf of each of the Secured Parties and will be first ranking.

5.2 The Security Agent will hold one set of Security for all of the Secured Parties unless a separate Security is required by local law for any class of the Secured Parties.

6. **General terms of the Security**

6.1 Where appropriate, defined terms in the Transaction Security Documents should mirror those in this Agreement.

6.2 The parties to this Agreement agree to negotiate the form of each Transaction Security Document in good faith and will ensure that all documentation required to be entered into as a condition precedent to first drawdown under this Agreement (or immediately thereafter) is in a finally agreed form as soon as reasonably practicable after the Original Effective

Date. The form of guarantee for each Original Guarantor is set out in Clause 19 (*Guarantee and indemnity*) of this Agreement and, with respect to any Additional Guarantor, the form of guarantee shall be subject to any limitations consistent with these Agreed Security Principles which shall be set out in the Accession Deed applicable to such Additional Guarantor.

6.3 The Security shall, to the extent possible under local law, be enforceable on the occurrence of a Declared Default.

6.4 Security will, where possible and practical, automatically create Security over future assets of the same type as those already secured.

6.5 Unless required by local law, the circumstances in which any guarantee or Security shall be released should not be dealt with in individual security documents.

6.6 Information such as lists of assets, will be provided if, and only to the extent, required by local law to be provided to perfect or register the security and, unless required to be provided by local law more frequently, be provided upon execution of a security document and thereafter:

(a) in the case of lists of accounts receivable, quarterly;

(b) in the case of lists of tangible assets, semi-annually; and

(c) in the case of other lists, annually,

or, following an Event of Default which is continuing, on the Security Agent's reasonable request.

7. **UNDERTAKINGS/REPRESENTATIONS AND WARRANTIES**

Any representations, warranties or undertakings which are required to be included in any Transaction Security Document shall reflect (to the extent to which the subject matter of such representation, warranty and undertaking is the same as the corresponding representation, warranty and undertaking in this Agreement) the commercial deal set out in this Agreement (save to the extent that Secured Parties' local counsel deem it necessary to include any further provisions (or deviate from those contained in this Agreement) in order to protect or preserve the Security granted to the Secured Parties).

8. **GOVERNING LAW**

8.1 Unless granted under a global security document governed by the law of the jurisdiction of an Obligor or under English law, all Security (other than share Security) shall be governed by the law of the jurisdiction of incorporation of that Obligor or, in the case of a US Obligor, the law of New York.

8.2 Security over shares shall be governed by the laws of the country in which the entity whose shares are being secured is incorporated, or, in the case of a US Obligor, the law of New York, and not by the laws of the country in which the Obligor granting the Security is incorporated.

9. SPECIFIC ASSET SECURITY

9.1 Bank accounts

(a) An Obligor shall grant Security over all of its bank accounts in existence at the Original Effective Date (and thereafter shall grant such security over future bank accounts but shall be free to deal with those accounts in the course of its business until a Declared Default, save in respect of cash collateral and mandatory prepayment holding accounts.

(b) If required by local law to perfect the Security, notice of the Security will be served on the account bank within five business days of the Security being granted and the Obligor shall use its reasonable endeavours to obtain the account bank's agreement in principle to acknowledge that notice and, subsequently, an acknowledgement of that notice.

(c) Any Security over bank accounts shall be subject to any prior security interests in favour of the account bank which are created either by law or in the standard terms and conditions of the account bank provided that such prior security interests must only secure fees and costs of such account bank. The notice of security must request these are waived by the account bank but the Obligor shall not be required to change its banking arrangements if these security interests are not waived or only partially waived.

(d) If required under local law security over bank accounts will be registered.

(e) The foregoing clauses (a) through (d) do not apply to bank accounts located in the United States. For any bank account maintained in the United States, (other than an Excluded Account), the applicable Obligor shall be required to provide a customary deposit account control agreement covering such bank account.

9.2 Insurance policies

(a) All insurance policies shall be charged in favour of the Secured Parties except for third party liability insurance and insurance in favour of employees (to the extent permissible by applicable law).

(b) Notice of the Security will be served on the insurance provider within five business days of the Security being granted and the Obligor shall use its reasonable endeavours to obtain the insurance provider's agreement in principle to acknowledge that notice and, subsequently, an acknowledgement of that notice.

9.3 Intellectual Property

(a) No Security shall be granted over any Intellectual Property which cannot be secured under the terms of the relevant licensing agreement (after taking into account any relevant provisions of applicable law that may override such anti-encumbrance provisions) provided that reasonable endeavours to obtain consent to charging any such Intellectual Property shall be used by the relevant Obligor if the relevant Intellectual Property right is material. Subject to the foregoing, no notice shall be prepared or given to any third party from whom Intellectual Property is licensed until an Event of Default.

(b) Security over Intellectual Property will be registered at the relevant registry in the United States in accordance with the terms of any New York law security

agreement. No registrations will be required at any other national or supra-national registry.

9.4 **Trade receivables**

(a) If an Obligor grants Security over its trade receivables it shall be free to deal with those receivables in the course of its business until the occurrence of a Declared Default.

(b) No notice of security may be served until the occurrence of a Declared Default.

(c) If required under local law Security over trade receivables will be registered.

(d) Any list of trade receivables required shall to the extent practicable include details of the underlying contracts and/or debtors to the extent reasonably considered necessary by the Security Agent.

9.5 **Shares**

(a) Each member of the Group shall grant a charge over the shares in its subsidiary if that subsidiary is an Obligor.

(b) Until the occurrence of a Declared Default, the Obligor executing a share charge will be permitted to retain and to exercise voting rights to any shares charged by it in a manner which does not adversely affect the validity or enforceability of the Security or cause an Event of Default to occur and the company whose shares have been charged will be permitted to pay dividends to the Obligor in those circumstances.

(c) Where customary or required by law, at the time of execution of the share charge, the share certificate and a stock transfer form executed in blank will be provided to the Security Agent and where required by law the share certificate or shareholders register will be endorsed or written up and the endorsed share certificate or a copy of the written up register provided to the Security Agent.

(d) Unless the restriction is required by law, the constitutional documents of the company whose shares have been charged will be amended to remove any restriction on the transfer or the registration of the transfer of the shares on enforcement of the Security granted over them.

9.6 **Real estate**

(a) Mortgages will be required only with respect to real property with a market value in excess of $5,000,000 (or its equivalent). No mortgages will be required in relation to leased property in the United States.

(b) Subject to Clause 23.33 (*Landlord waivers*), no Obligor will be required to obtain any landlord's consent.

SIGNATURES

[NOT RESTATED]

CERTAIN CONFIDENTIAL INFORMATION MARKED BY [***] HAS BEEN EXCLUDED FROM THIS EXHIBIT BECAUSE IT IS BOTH NOT MATERIAL AND IS THE TYPE THAT THE REGISTRANT TREATS AS PRIVATE OR CONFIDENTIAL.

AMENDMENT 1 TO THE MANUFACTURING AND TECHNOLOGY DEVELOPMENT MASTER AGREEMENT

This amendment is effective as of the date the last signature is made ("**Effective Date**") between **Orchard Therapeutics (Europe) Limited**, with registered offices 245 Hammersmith Road, 3rd Floor, London, W6 8PW, United Kingdom England, company number 09759506, (**OTL**) and **AGC Biologics S.p.A.** with registered offices at via Meucci 3, Bresso (MI) Italy (**AGC**)

WHEREAS

a) On July 2, 2020, OTL and AGC entered into a manufacturing and technology development master agreement (the "**MSA**");

b) The Parties wish to amend and restate i) the original Annex A (Viral Vector Manufacturing Fees) attached to Schedule 1 to the MSA; ii) the original Annex B (DP Manufacturing Fees: Clinical & Commercial) to Schedule 2 to the MSA and iii) Schedule 6 to the MSA;

c) In addition, the Parties wish to set forth their understanding with respect to the amount due by OTL for the additional costs borne by AGC in the performance of the Manufacturing Services under the MSA.

NOW, THEREFORE, in consideration of the foregoing premises and the mutual covenants and agreements provided herein, the parties hereto, intending to be legally bound hereby, agree as follows:

1. All capitalized terms not otherwise defined in this amendment shall have the meanings ascribed to them in the MSA and its schedules.

2. The Parties agree to amend and restate

    a. the original Annex A (Viral Vector Manufacturing Fees) attached to Schedule 1 to the MSA with the amended and restated Annex A (Viral Vector Manufacturing Fees) attached to this amendment;

    b. the original Annex B (DP Manufacturing Fees: Clinical & Commercial) attached to Schedule 2 to the MSA with the amended and restated Annex B (DP Manufacturing Fees: Clinical & Commercial) attached to this amendment;

    c. the original Schedule 6 to the MSA with the amended and restated Schedule 6 attached to this amendment.

3. In consideration of the additional testing performed on Libmeldy, MLD Clinical US and MLD Late Juvenile Drug Products manufactured as of 29 Jul 2021 and listed in Appendix 1 to this amendment, OTL shall pay AGC **[***]**.

4. In consideration of the additional costs borne by AGC for the increase of prices in DP Materials and VV Materials used for the Products manufactured as of January 1, 2022 and listed in Appendix 2 to this amendment, OTL shall pay AGC **[***]**.

5. AGC will invoice the total amount due pursuant to sections 3 and 4 above (**[***]**) upon signature of this amendment. OTL shall pay the invoice within thirty (30) days from the date of receipt of the invoice.

6. With reference to the actual external costs borne or to be borne by AGC for the external testing performed/to be performed by **[***]** on Viral Vectors and Drug Products manufactured as of January 1, 2022, AGC will provide OTL with the relevant quotation, in accordance with the confidentiality agreement signed on April 16, 2021 between AGC, OTL and **[***]**.

   AGC will track actual costs incurred by **[***]** in the performance of the external testing as detailed in the respective quotation and communicate in a timely manner to OTL any increase in cost. The parties agree to meet and discuss the increase and likely effect on actual costs to be borne by AGC and OTL. If reasonably requested by OTL, AGC agrees to enter negotiations with **[***]** to address the cost increase. If following reasonable efforts by the parties to address any increases, the actual costs borne by AGC are higher than the amount already paid by OTL, OTL shall provide AGC with a dedicated Purchase Order to cover such amount.

7. Except as amended by this amendment the MSA shall remain in full force and effect.

[*Signature Page Follows*]

Amended and restated Schedule 1 Annex A - Viral Vector Manufacturing Fees

[***]

AMENDED AND RESTATED SCHEDULE 6 – SPECIFIC EQUIPMENT

[***]

Exhibit 10.19

APPENDIX 1 to AMENDMENT 1 TO THE MANUFACTURING AND TECHNOLOGY DEVELOPMENT MASTER AGREEMENT –

[***]

Appendix 2 to the AMENDMENT 1 TO THE MANUFACTURING AND TECHNOLOGY DEVELOPMENT MASTER AGREEMENT

[***]

Exhibit 21.1

Subsidiaries

Name of Subsidiary	Jurisdiction of Incorporation or Organization
Orchard Therapeutics (Europe) Limited	England and Wales
Orchard Therapeutics North America	California (United States)
Orchard Therapeutics (Netherlands) B.V.	Netherlands
Orchard Therapeutics (France) SAS	France
Orchard Therapeutics (Italy) S.r.l	Italy
Orchard Therapeutics (Germany) GmbH	Germany
Orchard Therapeutics (Switzerland) GmbH	Switzerland
Orchard Therapeutics (Sweden) AB	Sweden

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-8 (Nos. 333-228067, 333-230432, 333-241646, 333-258446, and 333-266507) and Form S-3 (No. 333-263967) of Orchard Therapeutics plc of our report dated March 14, 2023 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
March 14, 2023

Exhibit 31.1

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, Bobby Gaspar, certify that:

1. I have reviewed this Annual Report on Form 10-K 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 registrant as of, and for, the periods presented in this report;

4. The registrant'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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant 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 registrant, 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

Date: March 14, 2023

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer

Exhibit 31.2

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 10-K 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 registrant as of, and for, the periods presented in this report;

4. The registrant'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)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant 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 registrant, 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) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant'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 registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer(s) and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant'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 registrant'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 registrant's internal control over financial reporting.

Date: March 14, 2023

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Orchard Therapeutics plc (the "Company") for the period ending December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 14, 2023

By: /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Orchard Therapeutics plc (the "Company") for the period ending December 31, 2022 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and result of operations of the Company.

Date: March 14, 2023

By: /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer