

**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, 2021

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
(State or other jurisdiction of
incorporation or organization)

Not Applicable
(I.R.S. Employer
Identification No.)

108 Cannon Street
London EC4N 6EU

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 Global Select 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	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
Emerging growth company	<input type="checkbox"/>		

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.

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 \$544 million.

As of March 15, 2022, the Registrant had 125,834,611 ordinary shares, nominal value £0.10 per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement for its 2022 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. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.
 - 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 OTL-200 for metachromatic leukodystrophy, or 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 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 preclinical 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. 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.
 - 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.
 - 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.
 - If we are unable to establish effective sales and marketing capabilities or enter into agreements with third parties to market, sell and gain reimbursement for Libmeldy and our product candidates that may be approved, we may be unable to generate product 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 and our business may suffer.
 - 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 products or product candidates.
 - Business interruptions resulting from the ongoing COVID-19 pandemic have caused and may continue to cause a disruption to the development of our product candidates and adversely impact our business.
 - We may not be able to protect our intellectual property rights throughout the world.
 - 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 effect on our business.
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- We have in the past, and in the future we may, enter into collaborations with third parties to develop or commercialize product candidates. If these collaborations are not successful, our business could be adversely affected.
- 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 preclinical studies for our programs and product candidates, including statements regarding the timing of initiation and completion of trials or studies and related preparatory work 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;
- 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

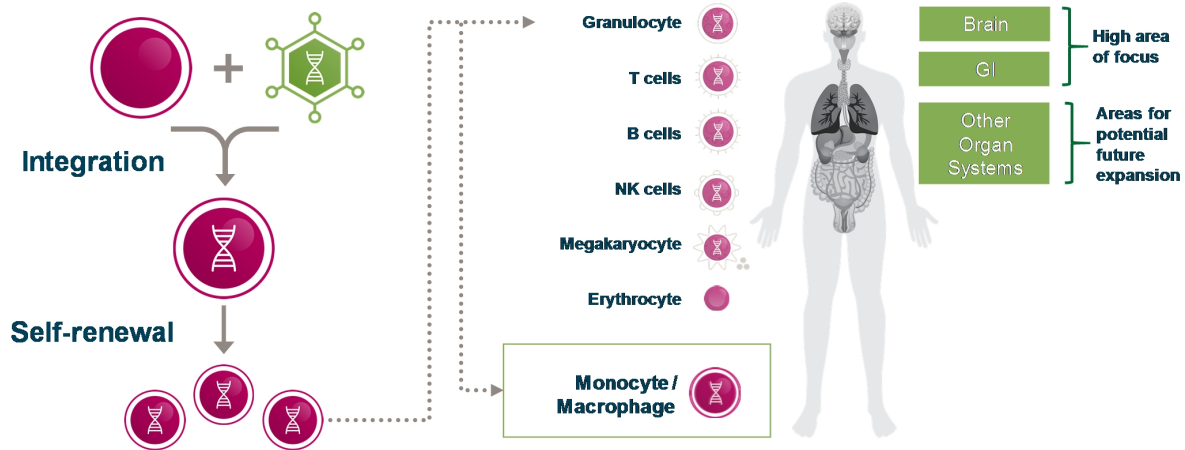
Item 1. Business.

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 160 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. Three eligible patients have been treated in a commercial setting to date. Our planned BLA submission timeline for OTL-200 with the FDA is late 2022 to early 2023.

We have a portfolio that includes a commercial-stage product and research and development-stage product candidates, and 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 are targeting 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. In anticipation of commercialization, 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 plan to deploy a focused 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. For example, in January 2021, we announced partnerships with two regional specialty pharmaceutical companies with experience in rare genetic diseases to support us in the Middle East and Turkey.

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, preclinical 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.

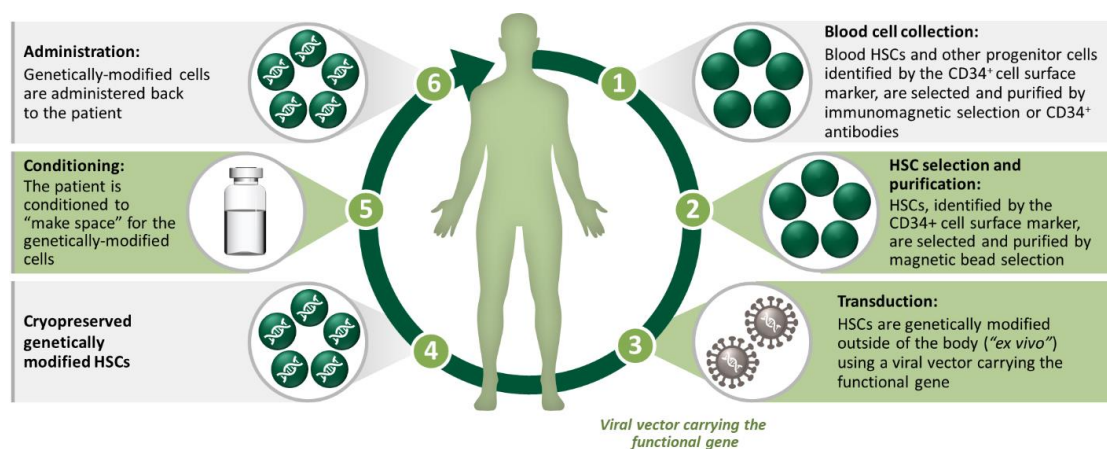
In a preclinical study conducted by one of our scientific advisors and published in *Proceedings of the National Academy of Sciences of the United States of America*, or *PNAS*, a subpopulation of gene-modified HSCs has evidenced the potential to cross the blood-brain barrier, engraft in the brain as 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.

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:

- Successfully commercialize Libmeldy (OTL-200) for the 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
- 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-III A, and three preclinical programs, OTL-202 for mucopolysaccharidosis type IIIB, or MPS-IIIB, OTL-204 for frontotemporal dementia with progranulin mutations, or GRN-FTD, and OTL-205 for amyotrophic lateral sclerosis, or ALS.
- Our programs in immunological disorders consist of two preclinical 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.
 - We also have a commercial program approved in Europe, Strimvelis for adenosine deaminase severe combined immunodeficiency, or 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 Strimvelis, OTL-103 and OTL-102.
 - 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 preclinical 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 have a program focused on blood disorders at the clinical proof of concept stage of development, OTL-300 for TDT. However, in May 2020, we announced that new investment in OTL-300 would be limited.

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.

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 timepoints 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 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 was based on the integrated analysis of results from 29 patients with early-onset MLD who were all treated with Libmeldy prepared as a fresh formulation:

- 20 patients were treated in a registrational 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 integrated efficacy analysis (described above)
- 6 patients treated with the cryopreserved formulation 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 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 ($IQ \geq 85$ 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 $100 \pm$ 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 WORLDSymposium 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 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 subpopulations 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.

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 in late 2022 or early 2023 using data from existing OTL-200 patients. This approach and timeline are subject to the successful completion of activities remaining in advance of an expected pre-BLA meeting with the FDA, including demonstration of the natural history data as a representative comparator for the treated population.

Gene therapy for treatment of MPS-I

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 3 major recognized clinical entities: Hurler, or MPS-IH, Scheie, or MPS-IS, and Hurler-Scheie, or MPS-IH/S, syndromes. Hurler and Scheie syndromes represent phenotypes at the severe and attenuated ends of the MPS-I clinical spectrum, respectively.

The median age of diagnosis for MPS-IH is 12 months; most affected children are diagnosed before 18 months of age. Infants affected by MPS-IH usually appear normal at birth, but may develop inguinal or umbilical hernias in the first six months, and develop 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 with 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 diagnosed before the age of 30 months and with presumed MPS-IH (presence of family history and/or clinical signs and symptoms compatible with MPS-IH, *i.e.*, phenotypic diagnosis based on clinical expertise), and/or homozygosity or compound heterozygosity for mutations associated with the severe phenotype. The recommendation that HSCT should be 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 potentially fatal graft versus host disease, or GvHD, particularly when the degree of matching between graft donor and recipient is low. Additionally, although it may stabilize cognitive decline, life-threatening or severely debilitating cognitive, neurological, orthopedic, cardiac, respiratory and ophthalmic manifestations of MPS-IH have been reported during long-term post-HSCT follow-up.

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

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 corrective cDNA. The OTL-203 mechanism of action addresses the disease pathophysiology by restoring enzymatic IDUA expression in peripheral and central body compartments as well as restoring microglia homeostasis and its neuroprotective effects against the neurotoxic effects of glycosaminoglycan, or GAG, accumulation in affected cells. We have obtained worldwide development and commercialization rights to OTL-203 from Telethon Foundation and San Raffaele Hospital.

Autologous cells may be genetically modified to constitutively express supra-normal levels of the therapeutic enzyme and become a quantitatively more effective source of functional enzyme than wild-type cells, possibly also at the level of the nervous system and bone.

The therapeutic potential of this approach for addressing the extensive nervous system manifestations of MPS-IH is based on the contribution of HSCs to the turnover of CNS-resident microglia, demonstrated both in physiological and pathological conditions. Since microglia have been implicated in the pathogenesis of a number of neurodegenerative conditions, including LSDs. These cells should be considered a primary target cell type in therapeutic strategies for LSD with neurologic involvement such as MPS-IH. Moreover, 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 avoids the risks of graft versus host disease.

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 35 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 November 2021, we announced data published in the *New England Journal of Medicine* evaluating the safety and efficacy of OTL-203. For this publication's last follow up of all patients (range between 12 and 24 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 terms of biomarker data, treatment demonstrated rapid and sustained metabolic correction with all patients achieving supra-physiological IDUA expression in dried blood spot samples at 12 months (a primary efficacy endpoint). Associated with this, the results demonstrated increased IDUA expression in the CSF, with reduction of GAGs in CSF and normalization of GAG levels in urine.

All eight patients treated with OTL-203 showed stable cognitive function, motor function and growth within or near the normal range at multiple data points post-treatment. For instance, stable cognitive performance was shown in all patients post-treatment, with follow-up ranging from six months to two years. Longitudinal growth that was within age-appropriate reference ranges was seen in all patients post-treatment, with follow-up ranging from nine months to two years. Furthermore, stable motor function was seen in all patients compared to pre-treatment, with follow-up ranging from nine months to 1.5 years, and improved range of motion (less joint stiffness) was also shown in all patients compared to pre-treatment, with follow-up ranging from nine months to 1.5 years.

We have been granted parallel scientific advice by the FDA and EMA on this program. We intend to seek the necessary regulatory clearance in mid-2022 to enable the initiation of the OTL-203 global registrational study by year end.

Gene therapy for treatment of MPS-IIIA and MPS-IIIB

Disease overviews

MPS-IIIA, also known as Sanfilippo syndrome type A, and MPS-IIIB, also known as Sanfilippo syndrome type B, are life-threatening metabolic diseases that cause 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-III A progress to a vegetative state. Life expectancy for patients with MPS-III A and MPS-III B is between 10 to 25 years and 15 to 30 years, respectively.

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

Limitations of current therapies

Currently, there are no effective treatments or approved therapies for MPS-III A or MPS-III B. 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-III A and MPS-III B 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-III A and MPS-III B patients, their caregivers and families and healthcare systems.

Our solutions, OTL-201 for treatment of MPS-III A and OTL-202 for treatment of MPS-III B

We are developing OTL-201 and OTL-202 as *ex vivo* autologous HSC gene therapies for treatment of patients with MPS-III A and MPS-III B, respectively. In both indications we believe preclinical studies in mice have shown that *ex vivo* autologous gene therapy has the potential to address the neurological manifestations of MPS-III A and MPS-III B. We have obtained worldwide development and commercialization rights to OTL-201 and OTL-202 from The University of Manchester.

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

Proof of concept trial in MPS-III A

We are supporting a proof-of-concept trial for the treatment of MPS-III A, 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.

Interim results were presented at the WORLDSymposium in February 2022 through an oral presentation. The presentation featured supportive biomarker data from all five patients with evaluable results, with duration of follow-up ranging from three to 18 months. The treatment has been generally well-tolerated in all enrolled patients (n=5) with no serious adverse events.

In terms of biomarker data, SGSH enzyme expression in leukocytes and CD15+ cells increased from below normal levels at baseline to supra-physiological levels at three months in all five patients. Furthermore, investigators reported that within three months, there was >90% reduction in urinary GAGs (heparan sulfate) in all treated patients. Levels continue to decrease throughout the length of follow-up. CSF GAGs (heparan sulfate) decreased from baseline in the first three patients with available data.

We intend to report clinical data, including early clinical outcomes of cognitive function, from the OTL-201 proof-of-concept trial by year end.

Preclinical development of OTL-202 for treatment of MPS-III B

We intend to use the same approach to development for OTL-202 as OTL-201. Lentivirus vector optimization for OTL-202 for treatment of MPS-III B is ongoing, and we plan to continue to progress preclinical development of OTL-202. We plan to leverage information gained from OTL-201 preclinical and clinical development to support the OTL-202 program.

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/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.

Preclinical 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 preclinical 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.

We intend to report data from the preclinical proof-of-concept study by year end and file an IND in 2024.

Research program in ALS

Disease overview

Amyotrophic lateral sclerosis, or ALS, is a progressive neurodegenerative disease of the motor neurons. People affected by ALS develop muscular weakness, twitching and atrophy that cause difficulties in speaking, swallowing and eventually breathing. Mutations in many different genes have been linked to ALS and these generally lead to the malfunctioning of neurons and their degeneration, causing a strong inflammation in the brain that further worsen neuronal death. Microglia cells are a type of brain cells that are heavily involved in inflammation and can contribute to neuronal loss by promoting oxidative stress. In particular, the Nox2 gene expressed by microglia cells induces the production of reactive oxygen radical species, which cause oxidative stress, damage to molecules and inflammation. It is important to note that ALS patients who have lower levels of Nox2 have a much better survival.

The incidence of ALS is currently estimated at 2.1 to 3.8 per 100,000 live births in the EU and UK and 1.0 to 2.6 per 100,000 live births in the U.S., for a total of up to 12,000 to 15,000 new patients per year.

Limitations of current therapies

There is no effective treatment for ALS and the average survival is between two and four years from the onset of symptoms.

Our solution, OTL-205 for treatment of ALS

OTL-205 is an *ex vivo* autologous gene therapy being developed to genetically modify microglia cells so that they have a much lower level of Nox2 and therefore produce less oxidative stress and less local inflammation. Microglia cells can be derived from HSCs. In our approach, HSCs are extracted from the patient, modified in the laboratory with the lentiviral vector and then infused back into the patient. These modified HSCs then migrate into the brain, where they become microglia cells replacing the diseased cells and reducing inflammation. This approach has the potential to improve symptoms and prolong survival in all ALS patients irrespective of their genetic mutations. OTL-205 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.

Preclinical development of OTL-205

Preliminary *in vitro* data have shown that reducing Nox2 levels by RNA interference in microglia cells efficiently reduces the inflammatory response in these cells and the production of oxygen radicals.

We plan to continue to progress *in vitro* and *in vivo* characterization of this therapeutic approach in relevant ALS mouse models.

Immunological Disorders

Research program in NOD2-Crohn's Disease

Disease overview

Crohn's Disease, or CD, is a form of Irritable 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 amongst 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 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. We own pending patent applications in the United States and other jurisdictions and all other intellectual property rights associated with the OTL-104 program.

Preclinical development of OTL-104

OTL-104 preclinical work has shown that restoration of NOD2 gene expression in murine and human stem cells can rescue a defective myeloid immune response to microbial peptides. NOD2 defective inflammatory functions in primary human myeloid cells can be restored by both lentiviral and gene editing approaches. Preclinical studies to evaluate the safety of this approach show that NOD2-LV gene modification of human CD34⁺ stem cells does not affect HSC engraftment or immune subset development and differentiation following transplantation into NSG mice. Transplantation of NOD2-LV gene modified murine stem cells further demonstrates that HSC derived transgene⁺ cells can efficiently migrate and reconstitute the myeloid cell compartments of intestinal tissue.

Development of an experimental colitis induction model is now in progress for OTL-104 preclinical proof-of-concept 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.

Blood disorders

Gene therapy for treatment of TDT

In May 2020, we announced that new investment in OTL-300 for treatment of beta-thalassemia would be limited.

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, either on our own or with partners. We are building research capabilities to continue to explore additional indications in our laboratories.

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 judgement 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 purposes of this Annual Report we refer to these clinical trials as supportive clinical trials. In addition, certain of our product candidates may be evaluated in clinical trials for which clinical data is not intended to be pooled with data from our registrational trials for purposes of a regulatory submission, but will be submitted to the applicable regulatory agencies for informational purposes. For purposes of this Annual Report we refer to these trials as additional clinical trials. In addition, in some cases patients may be ineligible for participation in our clinical trials and may receive treatment under a compassionate use program 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. See *Item 1A. Risk Factors*—“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,” “We may be unable to demonstrate comparability between drug product manufactured using HSCs derived from the patient’s mobilized peripheral blood and drug product manufactured using HSCs derived from the patient’s bone marrow and/or comparability between drug product that has been cryopreserved and fresh drug product and/or demonstrate comparability between the manufacturing process used at academic centers with the manufacturing process used at CDMOs,” and “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.”

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/or 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 lifecycle 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 and OTL-103 programs and expect to demonstrate comparability of our cryopreserved formulations to earlier manufactured fresh formulations in support of future submissions for marketing approval in the United States and Europe. Our programs in OTL-102, 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 commercially 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 substantially completed our build-out of our commercial operations in Europe with the goal of delivering Libmeldy to patients through qualified treatment centers in the UK, France, Germany, Italy and the Netherlands. In addition, we expect to leverage cross-border and treatment abroad reimbursement pathways in both Europe and markets such as the Middle East and Turkey through third-party strategic partners and distributors. Subject to approval of OTL-200 from the FDA, we plan to also put in place commercial operations and quality treatment centers in the U.S.

We have begun a phased build of 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 pilot studies for newborns in certain countries to screen for MLD and develop the necessary data package to enable universal newborn screening in various countries where we expect our products to be sold. Ultimately, we intend to utilize the commercial infrastructure that we are building to support the potential for multiple product launches, if approved, across multiple geographies. For many territories and countries, we may also elect to utilize strategic partners, distributors, or contract field-based teams to assist in the commercialization of our products.

We anticipate the list price of Libmeldy to be less than the average 10-year cumulative cost for some chronic or lifelong rare disease treatments, such as certain enzyme replacement therapies, which do not offer the potential for full genetic correction or a potentially positive impact on cognitive outcomes. We are engaging with European country- and regional-level payment authorities to negotiate reimbursement and access and are considering novel payment approaches, such as annuity payments, as part of these negotiation discussions.

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, Strimvelis 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 Strimvelis, OTL-103, OTL-200 and OTL-300, 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 Strimvelis, OTL-103, OTL-200 and OTL-300 and know-how, including other clinical data and production information relating to Strimvelis, OTL-103, OTL-200, and OTL-300.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we are seeking patent protection for our product candidates, the patent term is 20 years from the earliest date of filing a non-provisional patent application. In the United States, the term of a patent may be lengthened by a patent term adjustment 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 to us its portfolio of approved and investigational rare disease gene therapies, including Strimvelis, the first gene therapy approved by the EMA for ADA-SCID, two late-stage clinical gene therapy programs in ongoing registrational trials, OTL-200 for MLD and OTL-103 for WAS, and OTL-300, a clinical-stage gene therapy program for TDT. In addition, GSK novated to us their R&D Agreement with Telethon-OSR.

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

Under the GSK Agreement we are also obligated to pay non-refundable royalties and milestone payments in relation to the gene therapy programs acquired. We will pay a mid-single-digit percentage royalty on the annual net sales of Strimvelis. We

will also pay tiered royalty rates at percentages from the mid-teens to the low twenties for the MLD and WAS products, upon marketing approval, calculated as percentages of aggregate cumulative net sales of the MLD and WAS products, respectively. We will pay a tiered royalty at percentages from the high single-digits to the low teens for the 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, we may pay up to £90.0 million in milestone payments upon achievement of certain sales milestones. Our royalty obligations with respect to MLD and WAS may be deferred for a certain period in the interest of prioritizing available capital to develop each product. Our royalty obligations are subject to reduction on a product-by-product basis in the event of market control by biosimilars and will expire in April 2048.

We may terminate our development or commercialization activities of any of the programs under the GSK Agreement upon the occurrence of an SAE, if we believe such program poses a safety risk to patients or 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 ADA-SCID, WAS, MLD and TDT and options on three additional earlier-stage development programs.

Pursuant to the R&D Agreement, Telethon-OSR had granted to GSK an exclusive, worldwide, sublicensable license under certain intellectual property rights to develop and commercialize *ex vivo* gene therapy products for the treatment of ADA-SCID. In addition, Telethon-OSR had granted to GSK an exclusive option for an exclusive, sublicensable, worldwide license under certain intellectual property rights to develop and commercialize certain vectors and gene therapy products from disease-specific development programs for the treatment of WAS, MLD and TDT. 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 the WAS, MLD and TDT programs. We acquired Strimvelis and GSK's exclusive licenses relating to the ADA-SCID, WAS, MLD and TDT collaboration programs 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 (\$35.0 million at December 31, 2021) in connection with product development milestones with respect to those programs for which we have exercised an option under this agreement (that is, our WAS, MLD and TDT programs). Additionally, we are required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on net annual sales of licensed products on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third party sublicensees of the collaboration programs. Our royalty obligation expires on a licensed product-by-licensed product and country-by-country basis upon the latest to occur of the expiration of the last valid claim under the licensed patent rights in such country, the 10th anniversary of the first commercial sale of such licensed product in such country, and the expiration of any applicable regulatory exclusivity in such country, provided that our royalty obligation will terminate immediately in the event significant generic or biosimilar competition to a licensed product achieves

a certain threshold percentage of the market share.

Unless terminated earlier, the R&D Agreement will expire (i) on a product-by-product and country-by-country basis upon the expiration of all payment obligations with respect to such product in such country, (ii) in its entirety upon the expiration of all payment obligations with respect to the last product in all countries in the world, and (iii) on a program-by-program basis when no vector or gene therapy product is being researched, developed or commercialized. Either we or Telethon-OSR may terminate the R&D Agreement in its entirety or on a program-by-program basis if the other party commits a material breach and fails to cure such breach within a certain period of time. Additionally, either we or Telethon-OSR may terminate involvement in a collaboration program for compelling safety reasons, and either we or Telethon-OSR may terminate the R&D Agreement if the other party becomes insolvent. We may also terminate the R&D Agreement either in its entirety or on a program-by-program basis for any reason upon notice to Telethon-OSR.

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

As consideration for the licenses granted under the agreement, we issued 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 preclinical stage of developing an *in vivo* AAV gene therapy for MLD delivered intravenously, Passage Bio has a preclinical development program for MLD, and Affinia has a preclinical 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 preclinical 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 preclinical 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-III A:** There are currently no effective disease modifying treatment options for patients with MPS-III A. We are aware of three gene therapy candidates in clinical development. Lysogene is developing an AAV gene therapy product administered through intracerebral injections, in a collaboration with Sarepta Therapeutics that is set to terminate in July 2022; Abeona Therapeutics is developing AAV gene therapy product administered intravenously; and Esteve is developing an AAV gene therapy administered through intracerebroventricular injection. Amicus Therapeutics is at the preclinical stage of developing an AAV gene therapy for MPS-III A. We are aware that JCR Pharmaceuticals and Denali Therapeutics each has a preclinical stage ERT program for MPS-III A.
- **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 preclinical stage in collaboration with Takeda.
- **ALS:** There are currently few approved treatment options for ALS, limited to riluzole and edaravone. Multiple companies are developing gene therapies for genetically defined populations of ALS. We are not aware of any companies developing therapies targeted to reduce expression of Nox2.
- **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 preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product biological characteristics, chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

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 preclinical 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 reapprove 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 timeframes 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 judgement and these requirements may differ in the U.S. and the European Union.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA, the NIH and the investigators for serious and unexpected adverse events, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any

specified period, if at all. The FDA or the sponsor, acting on its own or based on a recommendation from the sponsor's data safety monitoring board may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product has been associated with unexpected serious harm to patients.

Human gene therapy products are a new category of therapeutics. Because this is a relatively new and expanding area of novel therapeutic interventions, there can be no assurance as to the length of the study period, the number of patients the FDA will require to be enrolled in the studies in order to establish the safety, 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 by three months if the FDA requests or the BLA sponsor otherwise provides additional information or clarification regarding information already provided in the submission within the last three months before the PDUFA goal date.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe, 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 ongoing COVID-19 pandemic, restrictions preventing the conduct or completion of facility or clinical site inspections have led and may continue to lead 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 or 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. 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 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, including some regulatory exclusivity periods tied to patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of a pediatric study in accordance with an FDA-issued "Written Request" for such a study.

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

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 offer sponsors the possibility to choose between the requirements of the previous Directive and the new Regulation if the request for authorization of a clinical trial is submitted in the year after the new Regulation became applicable. If the sponsor chooses to submit under the previous Directive, the clinical trial continues to be governed by the Directive until three years after the new Regulation became applicable. If a clinical trial continues for more than three years after the Clinical Trials Regulation became applicable, the Clinical Trials Regulation will at that time begin to apply to the clinical trial. The new Regulation overhauls the current 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). 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 timeframe 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 timeframe 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 timeframe 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 European Union, Great Britain will no longer be covered by centralized marketing authorizations (under the Northern Ireland Protocol, centralized marketing authorizations will continue to be recognized in Northern Ireland). All medicinal products with a current centralized marketing authorization were automatically converted to Great Britain marketing authorizations on January 1, 2021. For a period of two years from January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, the UK medicines regulator, may 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.

Data and marketing exclusivity

The EEA also provides opportunities for market exclusivity. Upon receiving marketing authorization in the EEA, 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 preclinical 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 EEA. 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 a MAA with a complete independent data package of pharmaceutical tests, preclinical tests and clinical trials. There is, however, no

guarantee that a product will be considered by the European Union’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 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 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 MA. 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 the EU).

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 drug for which 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 (if any is in effect at the time of approval) 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 EEA 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 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 European Union. Although general requirements for advertising and promotion of medicinal products are established under European Union directives, the details are governed by regulations in each European Union Member State and can differ from one country to another.

Brexit and the Regulatory Framework in the UK

In June 2016, the electorate in the UK voted in favor of leaving the EU (commonly referred to as "Brexit"), and the UK formally left the EU on January 31, 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on December 31, 2020. However, the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 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 largely aligns with current EU regulations, however it is possible that these regimes will diverge 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.

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 “whistleblower” to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery;
- the anti-inducement law, which prohibits, among other things, the offering or giving of remuneration, which includes, without limitation, any transfer of items or services for free or for less than fair market value (with limited exceptions), to a Medicare or Medicaid beneficiary that the person knows or should know is likely to influence the beneficiary’s selection of a particular supplier of items or services reimbursable by a federal or state governmental program;
- HIPAA, which created new federal criminal statutes that prohibit knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the 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 on May 25, 2018. Further to Brexit on January 31, 2020 and the expiry of the subsequent transition period on December 31, 2020, the EU GDPR has been brought into UK law as the "UK GDPR". In the present document, references to "GDPR" are meant to include both the EU 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

A primary trend in the U.S. healthcare industry and elsewhere is cost containment. Government authorities and other payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medical products. For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or ACA, was enacted, which, among other things, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; introduced a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; extended the Medicaid Drug Rebate Program to utilization of prescriptions of individuals enrolled in Medicaid managed care plans; imposed mandatory discounts for certain Medicare Part D beneficiaries as a condition for manufacturers' outpatient drugs coverage under Medicare Part D; subjected drug manufacturers to new annual, nondeductible fees based on pharmaceutical companies' share of sales to federal healthcare programs; imposed a new federal excise tax on the sale of certain medical devices; expanded healthcare fraud and abuse laws, including the False Claims Act and the Anti-Kickback Statute, new government investigative powers and enhanced penalties for non-compliance; expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; expanded the entities eligible for discounts under the PHS Act's pharmaceutical pricing program, also known as the 340B Drug Pricing Program; created new requirements to report financial arrangements with physicians and teaching hospitals, commonly referred to as the Physician Payments Sunshine Act; created a new requirement to annually report the identity and quantity of drug samples that manufacturers and authorized distributors of record provide to physicians; created a new Patient Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established the Center for Medicare Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Some of the provisions of the ACA have yet to be implemented, and there have been legal and political challenges to certain aspects of the ACA. Since its enactment, there have been judicial, Congressional and executive challenges to certain aspects of the ACA. In June 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is unclear how other healthcare reform measures of the Biden administration or other efforts, if any, to challenge, repeal or replace the ACA will impact our business.

Prior to the Biden administration, in October 2017, former President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. The former Trump administration concluded that cost-sharing reduction, or CSR, payments to insurance companies required under the ACA have not received necessary appropriations from Congress and announced that it will discontinue these payments immediately until those appropriations are made. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. On August 14, 2020, the U.S. Court of Appeals for the Federal Circuit ruled in two separate cases that the federal government is liable for the full amount of unpaid CSRs for the years preceding and including 2017. For CSR claims made by health insurance companies for years 2018 and later, further litigation will be required to determine the amounts due, if any. Further, on June 14, 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay more than \$12 billion in ACA risk corridor payments to third-party payors who argued the payments were owed to them. On April 27, 2020, the United States Supreme Court reversed the U.S. Court of Appeals for the Federal Circuit's decision and remanded the case to the U.S. Court of Federal Claims, concluding the government has an obligation to pay these risk corridor payments under the relevant

formula. It is unclear what impact these rulings will have on our business.

In addition, CMS published a final rule that would give states greater flexibility as of 2020 in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

On December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repeals the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future. Other legislative changes have been proposed and adopted since the ACA was enacted:

- In August 2011, President Obama signed into law the Budget Control Act of 2011, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals in spending reductions. The Joint Select Committee on Deficit Reduction did not achieve a targeted deficit reduction of at least \$1.2 trillion for fiscal years 2012 through 2021, triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which went into effect beginning on April 1, 2013 and, due to legislation amendments to the statute, including the BBA, will stay in effect through 2030 unless additional Congressional action is taken. However, pursuant to the Coronavirus Aid, Relief and Economic Security Act, or CARES Act, and subsequent legislation, these Medicare sequester reductions are suspended from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic. Following the temporary suspension, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.
- In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.
- On April 13, 2017, CMS published a final rule that gives states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.
- On May 30, 2018, the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.
- On May 23, 2019, CMS published a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs beginning January 1, 2020.
- On December 20, 2019, former President Trump signed into law the Further Consolidated Appropriations Act (H.R. 1865), which repealed the Cadillac tax, the health insurance provider tax, and the medical device excise tax. It is impossible to determine whether similar taxes could be instated in the future.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. At the federal level, the Trump administration's budget proposal for fiscal year 2021 includes a \$135 billion allowance to support legislative proposals seeking to reduce drug prices, increase competition, lower out-of-pocket drug costs for patients, and increase patient access to lower-cost generic and biosimilar drugs. On March 10, 2020, the Trump administration sent "principles" for drug pricing to Congress, calling for legislation that would, among other things, cap Medicare Part D beneficiary out-of-pocket pharmacy expenses, provide an option to cap Medicare Part D beneficiary monthly out-of-pocket expenses, and place limits on pharmaceutical price increases. Further, the Trump administration also previously released a "Blueprint", or plan, to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. HHS has already started the process of soliciting feedback on some of these measures and, at the same, is immediately implementing others under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy, a type of prior authorization, for Part B drugs beginning January 1, 2020. This final rule codified CMS's policy change that became effective January 1, 2019. In

addition, there has been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B drug pricing program, and CMS subsequently altered the FYs 2019 and 2018 reimbursement formula on specified covered outpatient drugs (“SCODs”). The court ruled this change was not an “adjustment” which was within the Secretary’s discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court’s decision and found that the changes were within the Secretary’s authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), but was denied on October 16, 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On Friday July 2, 2021, the Supreme Court granted the petition. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any. While a number of these and other proposed measures will require authorization through additional legislation to become effective, Congress has indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Additionally, there has been increasing legislative and enforcement interest in the United States with respect to drug pricing practices. Specifically, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, and review the relationship between pricing and manufacturer patient programs. At a federal level, President Biden signed an Executive Order on July 9, 2021 affirming the administration’s policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars; and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order also directs HHS to provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the Federal government pays for drugs, and address price gouging in the industry; and directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA’s implementing regulations. FDA released such implementing regulations on September 24, 2020, which went into effect on November 30, 2020, providing guidance for states to build and submit importation plans for drugs from Canada. On September 25, 2020, CMS stated drugs imported by states under this rule will not be eligible for federal rebates under Section 1927 of the Social Security Act and manufacturers would not report these drugs for “best price” or Average Manufacturer Price purposes. Since these drugs are not considered covered outpatient drugs, CMS further stated it will not publish a National Average Drug Acquisition Cost for these drugs. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. Further, on November 20, 2020 CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been calculated for certain drugs and biologics based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Additionally, on November 30, 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that they will continue to seek new legislative measures to control drug costs.

Individual states in the United States have also increasingly passed legislation and implemented regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

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. Further, due to the COVID-19 pandemic, millions of individuals have lost or may lose employer-based insurance coverage, which may adversely affect our ability to commercialize our products in certain jurisdictions.

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 and medical devices will likely continue as countries attempt to manage healthcare expenditures.

Employees and Human Capital Resources

As of December 31, 2021, we had 259 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, working remotely and implementing 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 108 Cannon Street, London EC4N 6EU, 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 \$144.6 million and \$152.0 million for the years ended December 31, 2021 and 2020, respectively. We historically have financed our operations primarily through private placements of our convertible preferred shares and through sales of our ADSs in our initial public offering and follow-on offering. We have devoted substantially all of our efforts to research and development, including clinical and preclinical development and arranging the manufacturing of our product candidates, establishing a commercial infrastructure to support the commercialization of Libmeldy in the European Union, building a global commercial infrastructure to support commercialization of Libmeldy (OTL-200) and our product candidates, if approved, as well as expanding our team. Prior to the approval of Libmeldy in Europe in December 2020, Strimvelis was our only product approved for sale, and in March 2022, we announced our decision to discontinue our investment in and seek alternatives for Strimvelis. Absent the realization of sufficient revenues from product sales of Libmeldy and Strimvelis, 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 deprioritized programs;
- conduct investigational new drug application, or IND, or clinical trial application, or CTA, enabling studies for our preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates 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 preclinical 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 Strimvelis and

Libmeldy. There is no assurance that revenue from sales of Libmeldy and Strimvelis 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 preclinical 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 revenues that are significant or large enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

We have only generated 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 revenues from product sales depends heavily on our and or our collaborators' success in:

- completing research and preclinical development of our product candidates and identifying 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 during the COVID-19 pandemic;
- 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, Strimvelis and our product candidates, if approved, as viable treatment options with acceptable safety profiles;
- addressing any competing technological and market developments;
- implementing additional internal systems and infrastructure, as needed, including robust quality systems and 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 we are required by the United States Food and Drug Administration, or the FDA, or the EMA or other regulatory authorities to perform clinical and other studies in addition to those that we currently anticipate or if we encounter delays or clinical holds in the development of our product candidates. Even if we generate more significant revenue from sales of Strimvelis and Libmeldy in Europe and are able to generate revenues from the sale of any other approved products, we may not become profitable and may need to obtain additional funding to continue operations.

We will need additional funding, which may not be available on acceptable terms or at all. Failure to obtain 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. We recorded negative cash flows from operating activities in 2021, primarily due to our net loss of \$144.6 million for that year. 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, preclinical 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, including our ability to resolve delays in trial enrollment as a result of the COVID-19 pandemic;
- 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, Strimvelis and any other products for which we may obtain marketing approval, including amounts reimbursed by government and third-party payors;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the terms of our current and any future license agreements and collaborations; and
- the extent to which we acquire or in-license other product candidates, technologies and intellectual property.

Identifying potential product candidates and conducting preclinical testing and clinical trials, 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 Strimvelis. In addition, Libmeldy, Strimvelis and any other products for which we obtain and maintain marketing approval may not achieve commercial success. Any product revenues from our product candidates, if any, will be derived from or based on sales of products that may not be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

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

We may seek to raise capital through a combination of public and private equity offerings, debt financings, strategic partnerships and alliances and licensing arrangements. To the extent that we raise capital through the sale of equity, convertible debt securities or other equity-based derivative securities, ownership percentages of all our shareholders may be diluted and the terms may include liquidation or other preferences that adversely affect their rights as shareholders. Any 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. The significant volatility in public equity markets and the disruptions to the U.S. and global economies caused by the COVID-19 pandemic 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 preclinical studies and planning and supporting clinical trials of our product candidates, establishing research and development and manufacturing capabilities, establishing a quality management system, establishing a commercial infrastructure to support the commercialization of Strimvelis in the European Union and building a global commercial infrastructure to support commercialization of Libmeldy. We have not yet demonstrated the ability to manufacture products on a commercial scale or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions about our future success or viability may not be as accurate as they 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.

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 the intended BLA submission, in which case the adequacy of our clinical endpoints, natural history analysis and CMC data package to support a potential BLA submission and approval will be review issues. 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 preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. There can be no assurance that the FDA, EMA or other foreign regulatory bodies will find the efficacy endpoints in our registrational trials or any efficacy endpoint we propose in future registrational trials to be sufficiently validated and clinically meaningful, or that our product candidates will achieve the pre-specified endpoints in current or future registrational trials to a degree of statistical significance, and with acceptable safety profiles. 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 preclinical studies or clinical trials prior to submitting or approving a BLA or MAA for our target indications.

It is possible that the FDA or 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 and/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 Tissues and Advanced Therapies within its Center for Biologics Evaluation and Research, or CBER, to consolidate the review of gene therapy and related products, and has established the Cellular, Tissue and Gene Therapies Advisory Committee to advise CBER in its review when called upon. 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 preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval. Similarly, the European Commission may issue new guidelines concerning the development and marketing authorization for gene therapies and require that we comply with these new guidelines, which could require additional preclinical studies or clinical trials to support the marketing approval of our product candidates or which could make our product candidates unable to successfully obtain approval.

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

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, Strimvelis and any other products for which we obtain marketing approval and could significantly harm our business, prospects, financial condition and results of operations.

To date, most of the clinical trials for our product candidates were conducted as investigator-sponsored clinical trials using drug product manufactured at 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 and/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 and/or drug product manufactured at such academic centers. Similarly, in those cases where clinical trials were conducted using fresh drug product, we will need to demonstrate comparability between drug product that has been cryopreserved and fresh drug product. In some cases, clinical trials were conducted using drug product using bone marrow or mobilized peripheral blood, or both, as the cellular source. In some cases, we may seek to demonstrate comparability between drug product manufactured using one cellular source and another. 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), preclinical studies and/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. For example, in connection with our OTL-200 (Libmeldy) program, the FDA has noted that we may have challenges demonstrating comparability between data collected at one manufacturing facility using bone marrow and data collected at another manufacturing facility using bone marrow or peripheral blood as source cells material.

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.

In certain conditions, such as MLD and ADA-SCID, the potency of a product candidate may be directly measured through enzymatic activity; however, for an intracellular protein such as WAS, developing an assay is more complex. Based on written feedback from the FDA, we believe that development of a functional potency assay for OTL-103 may require additional time and further investment. If an adequate potency assay for a product candidate is not available, if we face delays (including delays related to the COVID-19 pandemic), 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. In April 2020, the FDA advised us that we may need to generate additional data to demonstrate the comparability of our OTL-200 drug product derived from the patient's mobilized peripheral blood and the OTL-200 drug product derived from the patient's bone marrow, and that the data provided to date are inadequate to determine if the two materials are comparable. Further, the FDA requested that we provide data that demonstrates the comparability of the different OTL-200 product formulations used across our trials. Failure to demonstrate such comparability, or if we are required to conduct additional testing or additional clinical trials, potentially at additional sites, would delay any marketing authorization and adversely affect the commercial viability of our product candidates and may adversely affect our ability to generate revenue, as a result of which our business, prospects, financial condition and results of operations may suffer.

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

As part of our strategy, we intend to identify, develop and market additional product candidates beyond our existing product candidates. We may spend several years completing our development of any particular current or future product

candidates, and failure can occur at any stage. Even if we receive approval of a product candidate, we may not achieve commercial success for a variety of factors, including failure to achieve market acceptance in the medical community and the availability of third-party insurance coverage or reimbursement. For example, we received standard marketing authorization for Libmeldy in December 2020 from the European Commission and launched the commercialization of Libmeldy in Europe in early 2022, but there is no assurance that our commercialization efforts will be successful or that our pricing assumptions or our assumptions about the size of the anticipated patient population will prove to be accurate. The product candidates to which we allocate our resources may not end up being successful. Because we have limited resources, we may forego or delay pursuit of opportunities with certain programs or product candidates or for indications that later prove to have greater commercial potential. For example, in May 2020, we announced our decision to reduce investment in the development of OTL-101 for ADA-SCID (for which we subsequently terminated our license) and OTL-300 for TDT to focus on other product candidates in our pipeline and new research and development efforts in less rare diseases. Additionally, 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. 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 deprioritized product candidates, and if we choose to reprioritize such deprioritized 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. Our spending on current and future research and development programs may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential for a particular product candidate, we may relinquish valuable rights to that product candidate through strategic collaborations, licensing or other arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. If any of these events occur, we may be forced to abandon our development efforts with respect to a particular product candidate or fail to develop a potentially successful product candidate.

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

In addition, certain of our current or future product candidates may not demonstrate in patients any or all of the pharmacological benefits we believe they may possess or compare favorably to existing, approved therapies, such as 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. Accordingly, our focus on treating rare diseases may not always result in the discovery and development of commercially viable products.

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

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

From time to time, we may publish interim data and/or ad hoc analyses from investigator-sponsored or company-sponsored clinical trials of our product candidates. Preliminary data and ad hoc analyses from these clinical trials may change as 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 and/or more patient data become available to us. Interim, topline and preliminary data and ad hoc analyses also remain subject to audit and verification procedures that may result in the final data

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

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

For example, although sustained clinical activity has been observed in clinical trials to date for 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 preclinical studies. Our product candidates may fail to show the desired safety and efficacy in later stages of clinical development despite having successfully advanced through initial clinical trials. There can be no assurance that any of these trials will ultimately be successful or support further clinical advancement or regulatory approval of our product candidates. In addition, there can be no assurance that we will be able to achieve the same or similar success in our preclinical studies and clinical trials of our other product candidates.

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

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

We plan to submit any data available to us from compassionate use cases as part of any regulatory submission for the applicable product candidate. However, because these patients were not treated as part of a clinical trial 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 ongoing 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 pretreatment conditioning regimens;
- availability of competing therapies and clinical trials;
- severity of the disease under investigation;
- degree of progression of the subject's disease at the time of enrollment;
- availability of genetic testing for potential patients;
- proximity and availability of clinical trial sites for prospective subjects;
- 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. As a result of the COVID-19 global pandemic, certain of our clinical sites have partially shifted and may continue to shift significant resources to patients with COVID-19, which creates challenges for

patient follow-up visits for all programs. 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 recordkeeping requirements;
- failure to perform in accordance with the FDA's good clinical practices, or GCP, or applicable regulatory guidelines in other countries;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the clinical sites;
- delays in having patients complete participation in a study or return for post-treatment follow-up;
- clinical trial sites or patients dropping out of a study;
- 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 preclinical and clinical development could result in additional costs to us or impair our ability to generate revenues. In addition, if we make changes to our product candidates, we may need to conduct additional studies to bridge our modified product candidates to earlier versions, which could delay our clinical development plan or marketing approval for our product candidates. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates or allow our competitors to bring products to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business and results of operations.

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

- be delayed in obtaining marketing approval for our product candidates, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with, or later become subject to, labeling or a REMS (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 preclinical studies and clinical trials, we cannot predict when or if we will obtain regulatory approval to commercialize a product candidate, and the approval may be for a 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 preclinical testing and earlier-stage clinical trials. Additional delays may result if an FDA Advisory Committee or other regulatory authority recommends non-approval or restrictions on approval. In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action or changes in regulatory agency policy during the period of product development, clinical trials and the review process.

As of May 26, 2021, the FDA noted it was continuing to ensure timely reviews of applications for medical products during the COVID-19 pandemic in line with its user fee performance goals and conducting mission critical domestic and foreign inspections to ensure compliance of manufacturing facilities with FDA quality standards. However, the FDA may not be able to maintain this pace and delays or setbacks are possible in the future, including where a pre-approval inspection or an inspection of clinical sites is required and, due to the ongoing COVID-19 pandemic and travel restrictions, the FDA is unable to complete such required inspection during the review period. In 2020 and 2021, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may similarly experience delays in their regulatory activities due to the COVID-19 pandemic.

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

Our product candidates and the activities associated with their development and commercialization, including their design, testing, manufacture, safety, efficacy, recordkeeping, labeling, storage, approval, advertising, promotion, sale and distribution, export and import, are subject to comprehensive regulation by the FDA and other regulatory agencies in the United States and by the EMA and comparable regulatory authorities in other countries. Failure to obtain marketing approval for a product candidate will prevent us from commercializing such product candidate. We have only limited experience in submitting and supporting the applications necessary to gain marketing approvals and expect to rely on third-party CROs to assist us in this process.

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

The process of obtaining marketing approvals, both in the United States and abroad, is expensive (the submission fee in the United States can be more than \$2.0 million and may be higher in the future), may take many years if additional clinical trials are required, if approval is obtained at all, and can vary substantially based upon a variety of factors, including the type,

complexity and novelty of the product candidates involved. Changes in marketing approval policies during the development period, changes in or the enactment of additional statutes or regulations, or changes in regulatory review for each submitted product application, may cause delays in the approval or rejection of an application. The FDA and comparable authorities in other countries have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other studies. In addition, varying interpretations of the data obtained from preclinical and clinical testing could delay, limit or prevent marketing approval of a drug candidate. Any marketing approval of our product candidates that we, or any future collaborators, ultimately obtain may be limited or subject to restrictions or post-approval commitments that render the approved product not commercially viable.

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

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 preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for our products, if approved, is also subject to approval. We intend to submit an MAA to the EMA for approval of our product candidates in the European Union but obtaining such approval from the European Commission following the opinion of EMA is a lengthy and expensive process. Even if a product candidate is approved, the FDA or the European Commission may limit the indications for which the product may be marketed, require extensive warnings on the product labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Regulatory authorities in countries outside of the United States and the European Union also have requirements for approval of product candidates with which we must comply prior to marketing in those countries. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

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

Additionally, in June 2016, the UK held a referendum in which a majority of voters approved an exit from the EU, or Brexit, and the UK formally left the EU on January 31, 2020. There was a transition period during which EU pharmaceutical laws continued to apply to the UK, which expired on December 31, 2020. However, the EU and the UK have concluded a trade and cooperation agreement, or TCA, which was provisionally applicable since January 1, 2021 and has been formally applicable since May 1, 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 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. For example, we do not yet have an IND open in the United States for OTL-203 for MPS-IH or OTL-201 for MPS-III A. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of these data is subject to conditions imposed by the FDA, as noted in the risk factor immediately above. For example, the clinical trial must be well designed and conducted and performed by qualified investigators in accordance with ethical principles. The trial population must also adequately represent the U.S. population, and the data must be applicable to the U.S. population and U.S. medical practice in ways that the FDA deems clinically meaningful. In addition, while these clinical trials are subject to the applicable local laws, FDA acceptance of the data will depend on its determination that the trials also complied with all applicable U.S. laws and regulations. If the FDA does not accept the data from any trial that we conduct outside the United States, 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, without an IND open in the United States, we forego more frequent interactions and dialogue with FDA regarding the design and conduct of our trials as well as product comparability, which may delay or halt the development of our product candidates later in development should 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 United States, we are required to seek FDA acceptance of an IND for each of our product candidates. We cannot be sure any IND we submit to the FDA, or any similar CTA we submit in other countries, will be accepted. We may also be required to conduct additional preclinical testing prior to submitting an IND for any of our product candidates, and the results of any such testing may not be positive. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to a BLA submission and approval of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

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 and OTL-103 for WAS received RMAT designation from the FDA, and both OTL-300 for TDT 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 Strimvelis, OTL-200 for MLD, OTL-103 for WAS, 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 or life-threatening manifestations primarily affect individuals aged from birth to 18 years and the disease affects fewer than 200,000 individuals in the U.S. or affects more than 200,000 in the U.S. and for which there is no reasonable expectation that the cost of developing and making in the U.S. a drug for such disease or condition will be recovered from sales in the U.S. of such drug. Under the FDA’s Rare Pediatric Disease Priority Review Voucher, or PRV, program, upon the approval of a BLA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for a Rare Pediatric Disease PRV that can be used to obtain priority review for a subsequent new drug application or BLA. The PRV may be sold or transferred an unlimited number of times. Congress has extended the PRV program 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-103 for WAS, 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 each of Libmeldy, OTL-103 for WAS and OTL-300 for TDT 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 Libmeldy, OTL-103 for WAS and OTL-300 for TDT. 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), OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-IIIa from the FDA and EMA, for OTL-203 for MPS-IH from the FDA, and for OTL-300 for TDT from the EMA, but we may be unable to obtain orphan drug designation for our other product candidates, and, even if we obtain such designation, we may not be able to realize the benefits of such designation, including potential marketing exclusivity of our product candidates, if approved.

Regulatory authorities in some jurisdictions, including the United States and other major markets, may designate drugs intended to treat conditions or diseases affecting relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product candidate as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as having a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the EU, the EMA's Committee for Orphan Medicinal Products grants orphan designation to promote the development of products that are intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the EU. Additionally, orphan designation is granted for products intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely 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, OTL-103 for WAS, OTL-102 for X-CGD and OTL-201 for MPS-IIIa from the FDA and EMA, for OTL-203 for MPS-IH from the FDA, and for OTL-300 for TDT from the EMA. If we request orphan drug designation for any of our other product candidates, there can be no assurances that the FDA or EMA will grant any of our 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 or if the product is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity may be revoked if any regulatory agency determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the product to meet the needs of patients with the rare disease or condition.

Even if we obtain orphan drug exclusivity for a product candidate, that exclusivity may not effectively protect the product candidate from competition because different drugs can be approved for the same condition. In the United States, even after an orphan drug is approved, the FDA may subsequently approve another drug for the same condition if the FDA

concludes that the latter drug is not the same drug or is clinically superior in that it is shown to be safer, more effective or makes a major contribution to patient care. In the EEA, 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 preclinical or quality data may only be accepted if duly justified and only in the case of a product intended to be used in emergency situations in response to public health threats. Conditional marketing authorizations are valid for one year, on a renewable basis. The holder will be required to complete ongoing trials or to conduct new trials with a view to confirming that the benefit-risk balance is positive. In addition, specific obligations may be imposed in relation to the collection of pharmacovigilance data.

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

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

Libmeldy, Strimvelis and any of our product candidates for which we obtain regulatory approval will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record-keeping and submission of safety and other post-market information. 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, particularly in the early symptomatic early juvenile population. For an example of adverse event reporting, in October 2020 we notified the EMA and relevant local European regulatory authorities after we became aware that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with leukemia.

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 grant of marketing authorization, and marketing of such products following grant of authorization may result in administrative, civil, or criminal penalties. These penalties could include delays in or refusal to authorize the conduct of clinical trials or to grant marketing authorization, product withdrawals and recalls, product seizures, suspension, or variation of the marketing authorization, total or partial suspension of production, distribution, manufacturing, or clinical trials, operating restrictions, injunctions, suspension of licenses, fines, and criminal penalties.

In addition, EU legislation related to pharmacovigilance, or the assessment and monitoring of the safety of medicinal products, provides that 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 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. As a result of the COVID-19 global pandemic, some of our CDMOs have experienced, and may continue to experience, delays and other direct impacts at their manufacturing sites as a result of travel restrictions, shelter-in-place policies or restrictions and other disruptions caused by the pandemic.

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 timeframe 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.

Since March 2020 when foreign and domestic inspections of facilities were largely placed on hold, the FDA has been working to resume routine surveillance, bioresearch monitoring and pre-approval inspections on a prioritized basis. Since April 2021, the FDA has conducted limited inspections and employed remote interactive evaluations, using risk management methods, to meet user fee commitments and goal dates. Ongoing travel restrictions and other uncertainties continue to impact oversight operations both domestic and abroad and it is unclear when standard operational levels will resume. The FDA is continuing to complete mission-critical work, prioritize other higher-tiered inspectional needs (e.g., for-cause inspections), and carry out surveillance inspections using risk-based approaches for evaluating public health. Should FDA determine that an inspection is necessary for approval and an inspection cannot be completed during the review cycle due to restrictions on travel, and the FDA does not determine a remote interactive evaluation to be adequate, the agency has stated that it generally intends to issue, depending on the circumstances, a complete response letter or defer action on the application until an inspection can be completed. During the COVID-19 public health emergency, a number of companies announced receipt of complete response letters due to the FDA's inability to complete required inspections for their applications. Regulatory authorities outside the U.S. may adopt similar restrictions or other policy measures in response to the ongoing COVID-19 pandemic and may experience delays in their regulatory activities.

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 launch strategy, which could delay or prevent patients from receiving gene therapy treatments, if approved. For example, due to COVID-19-related travel restrictions, some in-person visits to qualify certain potential treatment centers were postponed or required to take place remotely. 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 and this event, should it happen, could adversely affect our business, financial condition, results of operations and prospects.

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

Given the nature of biologics manufacturing, there is a risk of microbial contamination. Any microbial contamination could adversely affect our ability to produce, release or administer our gene therapies on schedule and could, therefore, harm our results

of operations and cause reputational damage. Additionally, although our gene therapies are tested for microbial contamination prior to release, if a contaminated product was administered to a patient, it could result in harm to the patient.

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

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

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

We have entered into licensing and collaboration agreements with third parties, including the GSK Agreement, pursuant to which GSK transferred to us Strimvelis, Libmeldy (OTL-200), OTL-103 for WAS and OTL-300 for TDT. In addition, GSK novated to us their R&D and collaboration and license agreement, or the R&D Agreement, with Telethon-OSR. These agreements impose, and we expect that future license agreements will impose, various due diligence, milestone payment, royalty, insurance and other obligations on us. The termination of these agreements could result in our loss of rights to practice the intellectual property licensed to us under these agreements and could compromise our development and commercialization efforts for our current or any future product candidates.

We 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 preclinical 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 revenues from these arrangements will depend on our and our collaborators' abilities to successfully perform the functions assigned to each of us in these arrangements. Moreover, an unsuccessful outcome in any clinical trial for which our collaborator is responsible could be harmful to the public perception and prospects of our gene therapy platform.

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. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report apply to the activities of our collaborators.

We may in the future decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of additional 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, Strimvelis 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 preclinical 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 preclinical studies and clinical trials required to support approval of our product candidates or the FDA, EMA or other regulatory agencies may refuse to accept our clinical or preclinical data. In such instances, we may need to enter into an appropriate 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 and/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 nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider or the COVID-19 global pandemic or similar 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 preclinical studies and clinical trials, including in some instances sponsoring such clinical trials, and to monitor and manage data for our ongoing preclinical and clinical programs. For example, OTL-102 for X-CGD is currently being investigated in ongoing academic-sponsored clinical trials at Boston Children's Hospital, the NIH and UCLA in the United States, and GOSH in Europe. While we will have agreements governing the activities of our academic partners and CROs, we will control only certain aspects of their activities and have limited influence over their actual performance.

Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on these third parties does not relieve us of our regulatory responsibilities. We and our third-party contractors and CROs are required to comply with 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 revenues could be delayed.

We do not control the design or conduct of the academic-sponsored trials, and it is possible that the FDA or EMA will not view these academic-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. Such arrangements provide us certain information rights with respect to the academic-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the academic-sponsored trials. However, we do not have control over the timing and reporting of the data from academic-sponsored trials, nor do we own the data from the academic-sponsored trials. If we are unable to confirm or replicate the results from the academic-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development of OTL-201 for MPS-IIIa and 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 preclinical, manufacturing or clinical data generated by these academic-sponsored trials or our interpretation of preclinical,

manufacturing or clinical data from these academic-sponsored trials. If so, the FDA or EMA may require us to obtain and submit additional preclinical, manufacturing or clinical data.

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

We currently have relationships with a limited number of suppliers for the manufacturing of our viral vectors and drug 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 and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any such remedial measures imposed upon us or third parties with whom we contract could materially harm our business.

If we or any of our 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 preclinical studies and clinical trials may be delayed.

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

We currently depend on a limited number of suppliers and, in some instances, a sole supplier, for some of the components and equipment necessary for the production of our viral vectors and drug product. We cannot be sure that these suppliers will remain in business, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to produce these materials for our intended purpose. Our use of a sole or a limited number of suppliers of raw materials, components and finished goods exposes us to several risks, including disruptions in supply, price increases, late deliveries and an inability to meet customer demand. There are, in general, relatively few alternative sources of supply for these components, and, in some cases, no alternatives. These vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Establishing additional or replacement suppliers for these components could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. As a result of the COVID-19 pandemic, we may experience supply shortages from some of our suppliers. 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 are building out our commercial infrastructure for the commercialization of Libmeldy in Europe, but we have a limited marketing and sales team. In order to commercialize Libmeldy, Strimvelis and any other product candidates that may be approved, we must continue to build and expand, on a territory-by-territory basis, marketing, sales, distribution, managerial and other capabilities or make arrangements with third parties to perform these 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, Strimvelis and our product candidates. We do not have any issued patents covering Libmeldy, Strimvelis or 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/or data exclusivities in, for example, the United States and Europe, these exclusivities would not prevent another biopharmaceutical company from conducting its own clinical trials to develop and seek regulatory approval of a competitive product. We are not the only company that is developing and commercializing products using a lentiviral-based autologous *ex vivo* gene 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, Strimvelis or any of our product candidates, if approved, our product revenues 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 revenues 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 any regulatory approval for our product candidates, the commercial success of our product candidates will depend in part on the medical community, patients, and payors accepting gene therapy products in general, and our product candidates in particular, as effective, safe and cost-effective. Any product that we bring to the market may not gain market acceptance by physicians, patients, payors and others in the medical community. The degree of market acceptance of these product candidates, if approved for commercial sale, will depend on a number of factors, including:

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

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

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

We expect the cost of a single administration of gene therapy products, such as those we are developing, to be substantial, when and if they achieve market approval. 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 revenues 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 revenues 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 product candidates will be adversely affected. The manner and level at which reimbursement is provided for services

related to our product candidates (*e.g.*, for administration of our product to patients) is also important. Inadequate reimbursement for such services may lead to physician resistance and adversely affect our ability to market or sell our product candidates, if approved.

Risks related to the impact of COVID-19

Business interruptions resulting from the COVID-19 pandemic or similar public health crises have caused and may cause or continue to cause a disruption to the development of our product candidates and adversely impact our business.

Public health crises such as pandemics or similar outbreaks can adversely impact our business. The COVID-19 global pandemic has caused significant disruptions to the U.S. and global economies, has contributed to significant volatility and negative pressure in financial markets, and has led to the implementation of various responses, including government-imposed quarantines, travel restrictions and other public health safety measures, which have impacted various aspects of our business and our operations and are likely to continue to impact our operations. The extent to which the COVID-19 global pandemic impacts our operations, or those of our third-party partners, will depend on future developments, which are highly uncertain and cannot be predicted with confidence. Such developments include the duration of the pandemic and related disruptions, renewed outbreaks in the future, including different variants of the virus, the ability to distribute and deliver approved vaccines and boosters on a timely basis and the uptake and effectiveness of such vaccines, new information that may emerge concerning the severity of the pandemic and other actions to contain the coronavirus or treat its impact, among others.

In response to the pandemic, we implemented a work from home policy. Most of our administrative employees continue to work outside of our offices, and we have reduced on-site staff significantly and, in some cases, restricted on-site staff to only those required to execute certain laboratory and related support activities. Continued remote working could have a variety of impacts on our business, including increasing our cyber security risk, creating data accessibility concerns, and making us more susceptible to communication disruptions, any of which could adversely impact our business operations or delay necessary interactions with regulators, manufacturing sites and clinical trial sites. We may also experience difficulty in recruiting and onboarding new employees. In addition, as a result of continued or renewed restrictions, our on-site staff conducting research and development, preclinical studies, and manufacturing activities may not be able to access our laboratories or manufacturing space, and these core activities may be significantly limited or curtailed, possibly for an extended period of time.

We are conducting clinical trials for our product candidates in the United States and Europe, which are currently being affected by the COVID-19 pandemic and will likely continue to be affected. Our clinical sites have devoted significant resources to patients with COVID-19, which could limit their ability to enroll additional patients in ongoing clinical trials or follow-up with existing patients. Some factors from the COVID-19 pandemic that have delayed and may continue to delay or otherwise adversely affect enrollment in or the progress of our clinical trials for some or all of our product candidates, as well as our business generally, include:

- the potential diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators, hospitals or academic centers serving as our clinical trial sites and staff supporting the conduct of our clinical trials;
- limitations on travel that could interrupt treatment center qualification, key trial activities, such as clinical trial site initiations and monitoring, domestic and international travel by employees, contractors or patients to clinical trial sites, including any government-imposed travel restrictions or quarantines that may impact the ability or willingness of patients, employees or contractors to travel to our clinical trial sites or secure visas or entry permissions, any of which could delay or adversely impact the conduct or progress of our clinical trials;
- interruption in global shipping affecting the transport of clinical trial materials, such as patient samples, investigational drug product and conditioning drugs and other supplies used in our clinical trials;
- business disruptions caused by potential workplace, laboratory and office closures and an increased reliance on employees working from home, disruptions to or delays in ongoing laboratory experiments and operations, disruptions or delays in subleasing any leased facilities no longer required for our business operations, staffing shortages, travel limitations or mass transit disruptions, any of which could adversely impact our business operations or delay necessary interactions with local regulators, ethics committees and other important agencies and contractors;

- business disruptions involving our third parties on whom we rely, including CROs and other collaborators for the conduct of our clinical trials or our third-party suppliers or CDMOs, which could impact their ability to perform adequately or disrupt our supply chain; and
- changes in hospital or research institution policies or government regulations, which could delay or adversely impact our ability to conduct our clinical trials.

Trial procedures (particularly any procedures that may be deemed non-essential), patient dosing, shipment of our product candidates, distribution of clinical trial materials, study monitoring, site inspections and data analysis may be paused or delayed due to the above factors or other reasons related to the pandemic. Furthermore, if the coronavirus, including new variants of the virus, continues to spread, or recurs in the future, or if approved vaccines are not as effective as anticipated or are significantly delayed in being administered, some patients and clinical investigators may not be able to comply with clinical trial protocols or we may see increased rates of patients withdrawing from any planned clinical trial following enrollment, including as a result of contracting COVID-19 or travel limitations (whether voluntary or required), which may impede patient movement, affect access to trial sites, or interrupt healthcare services. Moreover, follow-up visits associated with our active clinical trials are in most cases being conducted using alternative data collection approaches due to COVID-19 travel and other trial site limitations. Though we are following the FDA, EMA and certain country-specific guidance on the management of clinical trials during the COVID-19 pandemic, we may also utilize other alternative approaches that may not be as effective as traditional approaches, and regulatory bodies, such as the FDA and EMA, may not approve such data collection techniques and may consider the data collected during the COVID-19 pandemic insufficient support for the relevant regulatory filings. Additionally, we have experienced and anticipate that the COVID-19 pandemic may continue to result in regulatory delays, such as delays in receiving regulatory advice, reviews of applications, or performance of inspections required for approvals. The pandemic may also result in greater regulatory uncertainty. For example, while the FDA and EMA have issued guidance to provide biopharmaceutical manufacturers greater flexibility in certain regulatory areas, including remote monitoring, protocol deviations and adverse event reporting, such flexibility may result in greater uncertainty regarding the expectations of such health authorities in relation to this guidance and the adequacy of the data collected during the COVID-19 pandemic to support regulatory filings. Any disruption or delay in our ability to complete preclinical and clinical development of our product candidates could impair our ability to successfully gain regulatory approval for and ultimately commercialize our product candidates and may harm our business and results of operations.

The extent and impact of such disruptions are currently unpredictable. Any prolongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development, study and regulatory submissions of our product candidates. The COVID-19 global pandemic may also result in interruption or delays in the operations of the FDA and EMA and other regulatory agencies, which could further delay our anticipated regulatory submissions and any potential approval of our product candidates.

In addition, the COVID-19 pandemic initially impacted our ability to generate revenue from the sale of Strimvelis, as Ospedale San Raffaele, Milan, Italy, the treatment site for Strimvelis, postponed scheduling and treating non-urgent patients with the therapy for approximately three months. Although we derive limited revenue from sales of Strimvelis, a prolonged postponement of treatments would significantly reduce our sole source of product revenue. The COVID-19 pandemic may also result in a diversion of payor or government resources away from health technology assessment, reimbursement or market access activities, which could delay our efforts to commercialize Libmeldy in the EU.

The extent to which the COVID-19 pandemic impacts 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 ultimate geographic spread of the 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 do not yet know the full extent of potential delays or impacts on our business, our clinical and regulatory activities, our research programs, healthcare systems or the global economy as a whole. 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.

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 have acquired rights to several programs and we may in the future acquire rights to additional programs. If we are unable to effectively manage these programs, our future results may suffer.

In April 2018, we acquired worldwide rights to Libmeldy (OTL-200), Strimvelis, OTL-103 for WAS and OTL-300 for TDT pursuant to the GSK Agreement. We further acquired worldwide rights to OTL-203 for MPS-IH in May 2019 pursuant to an exclusive licensing agreement with Telethon-OSR. These acquisitions significantly changed the composition of our operations, markets and product candidate mix, and we are continuing to adapt our organization to manage these programs. As an example, we have since announced the reduction of the investment in and scope of certain of these programs. Our future success depends, in part, on our ability to continue to address these changes, and, where necessary, to attract and retain new personnel that possess the requisite skills called for by these changes.

Our failure to adequately address the financial, operational or legal risks of any of our acquisitions could harm our business. Financial aspects of such future transactions that could alter our financial position or operating results include:

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

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

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

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

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

The use of our product candidates in clinical trials and the sale of Strimvelis 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. There is a risk that our product candidates may induce adverse events. For example, in October 2020, we were notified that a patient treated with Strimvelis under a compassionate use program in 2016 had been diagnosed with leukemia. Subsequent findings confirmed that the patient's leukemia was due to insertional oncogenesis attributable to treatment with Strimvelis, though the CHMP concluded that the risk-benefit balance remains favorable. If we cannot successfully defend against product liability claims, including any claims related to treatment with Strimvelis, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

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

We believe our product liability insurance coverage is sufficient in light of our current commercial and clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. We intend to expand our insurance coverage each time we commercialize an additional product, 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. If we lost any such person's services, our business may suffer. While we have entered into employment agreements with each of our executive officers, any of them could leave our employment at any time. We do not maintain "key person" insurance policies on the lives of these individuals or the lives of any of our other employees. The loss of the services of one or more of our current employees might impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining other qualified employees, consultants and advisors for our business, including scientific and technical personnel, will also be critical to our success. There is currently a shortage of skilled executives in our industry, which is likely to continue. As a result, competition for skilled personnel, including in gene therapy research and vector manufacturing, is intense and the turnover rate can be high. We may not be able to attract and retain personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for individuals with similar skill sets. In addition, failure to succeed in preclinical or clinical trials may make it more challenging to recruit and retain qualified personnel. The inability to recruit or the loss of the services of any executive, key employee, consultant or advisor may impede the progress of our research, development and commercialization objectives.

Our corporate restructuring and the associated proposed headcount reduction may not result in anticipated savings, could result in total costs and expenses that are greater than expected and could disrupt our business, and we may experience difficulties in managing our current and any future restructurings.

On March 30, 2022, we announced a proposed reduction of our workforce of approximately 30%, subject to a consultation process with certain employees in the United Kingdom. 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 growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Due to our limited resources, we may not be able to effectively manage our operations or recruit and retain qualified personnel, which may result in weaknesses in our infrastructure and operations, risks that we may not be able to comply with legal and regulatory requirements, and loss of

employees and reduced productivity among remaining employees. For example, the proposed workforce reduction may negatively impact our clinical, regulatory, technical operations, and commercial functions, which would have a negative impact on our ability to successfully develop, and ultimately, commercialize our product candidates. Our future financial performance and our ability to develop our product candidates or additional assets will depend, in part, on our ability to effectively manage any future growth or restructuring, as the case may be.

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.

Payors, whether domestic or foreign, or governmental or private, are developing increasingly sophisticated methods of controlling healthcare costs and those methods are not always specifically adapted for new technologies such as gene therapy and therapies addressing rare diseases such as those we are developing. In both the United States and certain foreign jurisdictions, there have been a number of legislative and regulatory changes to the health care system that could impact our ability to sell our products profitably. In particular, in 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively, the ACA, was enacted, which, among other things: (i) subjected biologic products to potential competition by lower-cost biosimilars; (ii) addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected; (iii) increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program; (iv) extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations; (v) subjected manufacturers to new annual fees and taxes for certain branded prescription drugs; (vi) created a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of January 1, 2019, or the BBA, point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; and (vii) provided incentives to programs that increase the federal government's comparative effectiveness research.

Some of the provisions of the ACA have yet to be fully implemented, while certain provisions have been subject to judicial and Congressional challenges. While Congress has not passed comprehensive repeal legislation, two bills affecting the implementation of certain taxes under the ACA have been signed into law. First, the Tax Cuts and Jobs Act of 2017, or the Tax Act, decreased the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, commonly referred to as the "individual mandate," to \$0, effective January 1, 2019. Second, the BBA repealed the so-called "Cadillac" tax on certain high-cost employer-sponsored

insurance plans, the annual fee imposed on certain health insurance providers, and the medical device excise tax on non-exempt medical devices. The BBA also closed the coverage gap in most Medicare drug plans, commonly referred to as the “donut hole.”

In June 2021, the U.S. Supreme Court, or Supreme Court, dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an Executive Order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The Executive Order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

In June 2018, the U.S. Court of Appeals for the Federal Circuit ruled that the federal government was not required to pay in excess of \$12.0 billion in ACA risk corridor payments to third-party payors. This decision was appealed to the Supreme Court, which in April 2020 reversed the U.S. Court of Appeals and remanded the case, concluding that the government had an obligation to pay these risk corridor payments under the relevant formula. The effects of this gap in reimbursement on third-party payors, the viability of the ACA marketplace, providers, and potentially our business are not yet known.

Further, in December 2018, CMS published a final rule permitting further collections and payments to and from certain ACA-qualified health plans and health insurance issuers under the ACA risk adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. Since then, the ACA risk adjustment program payment parameters have been updated annually. In addition, CMS published a final rule that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through such marketplaces.

It is unclear how other healthcare reform measures of the Biden administrations or other efforts, if any, to challenge repeal or replace the ACA, will impact our business.

Other legislative changes potentially affecting our business have been proposed and adopted in the United States since the ACA was enacted. In August 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least \$1.5 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This included aggregate reductions of Medicare payments to providers of 2% per fiscal year, which went into effect in April 2013 and will remain in effect through 2030 unless additional Congressional action is taken. Pursuant to the CARES Act and subsequent legislation, however, these reductions were suspended from May 2020 through March 31, 2022 due to the COVID-19 pandemic. Then, a 1% payment reduction will occur beginning April 1, 2022 through June 30, 2022, and the 2% payment reduction will resume on July 1, 2022.

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

In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain health care facilities. On December 27, 2018, the District Court for the District of Columbia invalidated a reimbursement formula change under the 340B drug pricing program, and CMS subsequently altered the FYs 2019 and 2018 reimbursement formula on specified covered outpatient drugs (“SCODs”). The court ruled this change was not an “adjustment” which was within the Secretary's discretion to make but was instead a fundamental change in the reimbursement calculation. However, most recently, on July 31, 2020, the U.S. Court of Appeals for the District of Columbia Circuit overturned the district court's decision and found that the changes were within the Secretary's authority. On September 14, 2020, the plaintiffs-appellees filed a Petition for Rehearing En Banc (i.e., before the full court), but was denied on October 16, 2020. Plaintiffs-appellees filed a petition for a writ of certiorari at the Supreme Court on February 10, 2021. On Friday July 2, 2021, the Supreme Court granted the petition. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

There have been several other actions taken at a federal level seeking to lower drug prices. At a federal level, President Biden signed an Executive Order in July 2021 affirming the administration's policy to (i) support legislative reforms that would lower the prices of prescription drug and biologics, including by allowing Medicare to negotiate drug prices, by imposing inflation caps, and, by supporting the development and market entry of lower-cost generic drugs and biosimilars and (ii) support the enactment of a public health insurance option. Among other things, the Executive Order directs HHS to

provide a report on actions to combat excessive pricing of prescription drugs, enhance the domestic drug supply chain, reduce the price that the U.S. federal government pays for drugs, and address price gouging in the industry. The Executive Order also directs the FDA to work with states and Indian Tribes that propose to develop section 804 Importation Programs in accordance with the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, and the FDA's implementing regulations. The FDA released such implementing regulations in September 2020, which went into effect in November 2020, providing guidance for states to build and submit importation plans for drugs from Canada. Further, in November 2020, CMS issued an Interim Final Rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates would have been calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and would have applied to all U.S. states and territories for a seven-year period beginning January 1, 2021 and ending December 31, 2027. However, on December 29, 2021 CMS rescinded the Most Favored Nations rule. Further, authorities in Canada have passed rules designed to safeguard the Canadian drug supply from shortages. If implemented, importation of drugs from Canada may materially and adversely affect the price we receive for any of our product candidates. Additionally, in December 2020, HHS published a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors have been delayed until January 1, 2026. Although a number of these and other proposed measures may require authorization through additional legislation to become effective, and the Biden administration may reverse or otherwise change these measures, both the Biden administration and Congress have indicated that it will continue to seek new legislative measures to control drug costs.

At the state level, legislatures are increasingly passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, or restrictions on certain product access, and marketing cost disclosure and transparency measures, which, in some cases, are designed to encourage importation from other countries and bulk purchasing.

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

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

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

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 whistleblower or qui tam actions, against individuals or entities for, among other things: knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent; knowingly making, using or causing to be made or used, a false statement of record material to a false or fraudulent claim or obligation to pay or transmit money or property to the federal government 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 “whistleblower” 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/or 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. After a delay, the CCPA became subject to enforcement as of July 1, 2020. Although clinical trial data and protected health information subject to HIPAA are currently exempt from CCPA, we may be subject to the CCPA with respect to other personal information regarding California residents. 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. Effective starting on January 1, 2023, 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 and/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 and/or changes in business practices and policies.

Following the UK's withdrawal from the EU on January 31, 2020 and the end of the transitional arrangements agreed between the UK and EU, as of January 1, 2021, the GDPR has been incorporated into UK domestic. UK-based organizations doing business in the EU will need to continue to comply with the 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. 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.

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 and require the registration of pharmaceutical sales representatives. State and foreign laws, including for example the GDPR, which became effective May 2018 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 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 revenues, 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 European and UK data protection laws. In June 2021, the European Commission issued new forms of standard contractual clauses for data transfers from controllers or processors in the EU/EEA (or otherwise subject to the EU GDPR) to controllers or processors established outside the EU/EEA (and not subject to the EU GDPR). The new standard contractual clauses replace the standard contractual clauses that were adopted previously under the Data Protection Directive. The UK is not subject to the European Commission's new standard contractual clauses but has published its own version of standard clauses, referred to as International Data Transfer

Agreement, which was laid before Parliament in February 2022, and, unless objections are raised, will enter into force in March 2022 to enable transfers originating from the UK. We will be required to implement these new safeguards when conducting restricted data transfers under the GDPR and doing so will require significant effort and cost.

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, and 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, including the substantial economic dislocation that has occurred and is likely to persist as a result of the impact of the COVID-19 global pandemic;
- 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, misclassification or other violations of labor law or other alleged conduct;
- difficulties associated with staffing and managing international operations, including differing labor relations;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geo-political actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods, 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 and/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 and/or that these patents are not valid. However, if these patents were enforced against us and defenses to such enforcement were unsuccessful, unless we obtain a license to these patents, which may not be available on commercially reasonable terms, or at all, we could be liable for damages and precluded from commercializing any products and product candidates that were ultimately held to infringe these patents, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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 that are important or necessary to the development of our technology and products and product candidates, including technology related to the manufacture and use of our products and product candidates. In particular, we do not own any patents or patent applications and have not in-licensed any issued patents related to Strimvelis, Libmeldy or any of our lead product candidates. We have in-licensed certain know-how and data from GSK and Telethon-OSR, relating to Strimvelis, OTL-103 for WAS, Libmeldy, and OTL-300 for TDT, certain know-how and data from Telethon-OSR relating to OTL-203 for MPS-IH, and certain other intellectual property for our clinical and preclinical 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.

Although our license rights from The Regents of the University of California, University College London, GSK, and Telethon-OSR, are exclusive, they are limited to particular fields, such as MLD, WAS or TDT, and are subject to certain retained rights. Absent an amendment or additional agreement, we may not have the right to use the in-licensed intellectual property, data, or know-how for one of our programs in another program. Furthermore, the licenses (including sublicenses) that we have or may enter into in the future may not provide rights to use such intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology, products and

product candidates. As a result, we may not be free to commercialize certain of our products or product candidates in fields or territories of interest to us. Furthermore, if the licenses are not exclusive in territories of interest to us, we may be unable to prevent competitors from developing and commercializing competitive products in territories included in our licenses. Licenses (including sublicenses) to additional third-party technology that may be required for our development programs may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business.

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

Our current license agreements impose, and we expect that future license agreements that we may enter into will impose, various obligations, including diligence and certain payment obligations. If we fail to satisfy our obligations, the 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 Strimvelis, Libmeldy or OTL-103. Many of our products and product candidates are in-licensed from third parties. Accordingly, in some cases, the availability and scope of potential patent protection is limited based on prior decisions by our licensors or the inventors, such as decisions on when to file patent applications or whether to file patent applications at all. Our or our licensors' failure to obtain, maintain, enforce or defend such intellectual property rights, for any reason, could allow third parties, in particular, other established and better-financed gene therapy companies having established development, manufacturing and distribution capabilities, to make competing products or impact our ability to develop, manufacture and market our products and product candidates, even if approved, on a commercially viable basis, if at all, which could have a material adverse effect on our business.

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

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

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

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

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

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

Filing, prosecuting, maintaining, defending and enforcing patents on products and product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be less extensive than those in the United States. 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, if issued, or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors may infringe, misappropriate or otherwise violate patents, trademarks, copyrights or other intellectual property that we own or 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, thereby impairing our ability to protect our products and product candidates.

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

The patent positions of companies engaged in the development and commercialization of biologics are particularly uncertain. Two cases involving diagnostic method claims and “gene patents” have been decided by the Supreme Court. 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 and/or invalidity positions, or paying to obtain a license to these claims. In any of the foregoing or in other situations involving third-party intellectual property rights, if we are unsuccessful in defending against claims of patent infringement,

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

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 is likely to continue to fluctuate significantly. The market price of our ADSs depends on a number of factors, some of which are beyond our control. In addition to the factors discussed in this “Item 1.A.—Risk Factors” and elsewhere in this Annual Report, these factors include:

- adverse results or delays in preclinical studies or clinical trials;
- reports of adverse events in other gene therapy products or clinical trials of such products;
- an inability to obtain additional funding;
- failure by us to successfully develop and commercialize our product candidates;
- failure by 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 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;
- 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 Global Select Market 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 or publish inaccurate or unfavorable research about our business, our ADS price and trading volume could decline.

The trading market for our ADSs depends in part on the research and reports that securities or industry analysts publish about us or our business. We do not have any control over these analysts. In the event one or more analysts downgrade our ADSs or change their opinion of our ADSs, our ADS price would likely decline. In addition, if one or more analysts cease

coverage of our company or fail to regularly publish reports on us, we could lose visibility in the financial markets, which could cause our ADS price or trading volume to decline.

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

Based upon our ordinary shares outstanding as of December 31, 2021, our executive officers, directors, greater than five percent shareholders and their affiliates beneficially own approximately 51% of our ordinary shares and ADSs. 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 depository may agree to amend the deposit agreement in any way we decide is necessary or advantageous to us or to the depository. Amendments may reflect, among other things, operational changes in the ADS program, legal developments affecting ADSs or changes in the terms of our business relationship with the depository. In the event that the terms of an amendment are materially disadvantageous to ADS holders, ADS holders will only receive 30 days' advance notice of the amendment, and no prior consent of the ADS holders is required under the deposit agreement. Furthermore, we may decide to direct the depository to terminate the ADS facility at any time for any reason. For example, terminations may occur when we decide to list our ordinary shares on a non-U.S. securities exchange and determine not to continue to sponsor an ADS facility or when we become the subject of a takeover or a going-private transaction. If the ADS facility will terminate, ADS holders will receive at least 30 days' prior notice, but no prior consent is required from them. Under the circumstances that we decide to make an amendment to the deposit agreement that is disadvantageous to ADS holders or terminate the deposit agreement, the ADS holders may choose to sell their ADSs or surrender their ADSs and become direct holders of the underlying ordinary shares, but 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 depository 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 depository opposed a jury trial demand based on the waiver, the court would determine whether the waiver was enforceable based on the facts and circumstances of that case in accordance with the applicable state and federal law. To our knowledge, the enforceability of a contractual pre-dispute jury trial waiver in connection with claims arising under the federal securities laws has not been finally adjudicated by the 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 depository in connection with matters arising under the deposit agreement or the ADSs, including claims under federal securities laws, such holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may have the effect of limiting and discouraging lawsuits against us and/or the depository. If a lawsuit is brought against us and/or the depository under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may result in different outcomes than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

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

Holders of our ADSs do not have the same voting rights as the holders of our ordinary shares and may not receive voting materials in time to be able to exercise the holder's right to vote.

Except as described in this Annual Report and our Quarterly Reports and 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 depository to vote the ordinary shares underlying their ADSs. Otherwise, holders of ADSs will not be able to exercise their right to vote unless they withdraw the ordinary shares underlying their ADSs to vote them in person or by proxy in accordance with applicable laws and regulations and our Articles of Association. Even so, ADS holders may not know about a meeting far enough in advance to withdraw those ordinary shares. If we ask for the instructions of holders of the ADSs, the depository, upon timely notice from us, will notify ADS holders of the upcoming vote and arrange to deliver our voting materials to them. Upon our request, the depository will

mail to holders a shareholder meeting notice that contains, among other things, a statement as to the manner in which voting instructions may be given. We cannot guarantee that ADS holders will receive the voting materials in time to ensure that they can instruct the depository to vote the ordinary shares underlying their ADSs. A shareholder is only entitled to participate in, and vote at, the meeting of shareholders, provided that it holds our ordinary shares as of the record date set for such meeting and otherwise complies with our Articles of Association. In addition, the depository'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 depository 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 depository 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, 2021, we had outstanding 125,674,095 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, 2021, 17,619,073 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 timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements. 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, 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 depository bank.
- Under English law, subject to certain exceptions and disapplications, each shareholder generally has preemptive rights to subscribe on a proportionate basis to any issuance of ordinary shares or rights to subscribe for, or to convert securities into, ordinary shares for cash. Under U.S. law, shareholders generally do not have preemptive rights unless specifically granted in the certificate of incorporation or otherwise.
- Under English law and our Articles of Association, certain matters require the approval of 75% of the shareholders who vote (in person or by proxy) on the relevant resolution (or on a poll of shareholders representing 75% of the ordinary shares voting (in person or by proxy)), including amendments to the Articles of

Association. This may make it more difficult for us to complete 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.

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, and/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/or 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 2021 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.

We do not believe that we were a PFIC in the 2021 taxable year. The determination of whether we are a PFIC is a fact-intensive determination made on an annual basis applying principles and methodologies that in some circumstances are unclear and subject to varying interpretation. The value of our assets would also be determined differently for the purposes of this determination if we were treated as a CFC, as discussed above. As a result, there can be no assurance regarding if we currently are treated as a PFIC or may be treated as a PFIC in the future. In addition, for our current and future taxable years, the total value of our assets for PFIC testing purposes may be determined in part by reference to the market price of our ordinary shares or ADSs from time to time, which may fluctuate considerably. Under the income test, our status as a PFIC depends on the composition of our income which will depend on the transactions we enter into in the future and our corporate structure. The composition of our income and assets is also affected by the spending of the cash we raise in any offering.

In certain circumstances, a U.S. holder of shares in a PFIC may alleviate some of the adverse tax consequences described above by making either a “qualified electing fund,” or QEF, election or a mark-to-market election (if our ordinary shares or ADSs constitute “marketable” securities under the Code), which each require the inclusion of a pro rata share of our income on a current basis. If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information necessary for U.S. holders to make a QEF election. 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, 2021, we had cumulative carryforward tax losses of \$506.2 million. Subject to numerous utilization criteria and restrictions (including those that limit the percentage of profits that can be reduced by carried forward losses and those that can restrict the use of carried forward losses where there is a change of ownership of more than half the ordinary shares of the Company and a major change in the nature, conduct or scale of the trade), we expect these to be eligible for carry forward and utilization against future operating profits. The use of loss carryforwards in relation to 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 eligible for inclusion within these tax credit cash rebate claims. Our eligibility to claim payable research and development tax credits may be limited or eliminated because we may no longer qualify as a small or medium-sized company. The U.K. Finance Act of 2021 introduced a cap on payable credit claims under the SME Program in excess of £20,000 with effect from April 2021 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.

We may benefit in the future from the United Kingdom's "patent box" regime, which allows certain profits attributable to revenues from patented products (and other qualifying income) to be taxed at an effective rate of 10%. We are the exclusive licensee or owner of several patent applications which, if issued, would cover our product candidates, and accordingly, future upfront fees, milestone fees, product revenues and royalties could be taxed at this tax rate. When taken in combination with the enhanced relief available on our research and development expenditures, we expect a long-term lower rate of corporation tax to apply to us. If, however, there are unexpected adverse changes to the 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. These adverse impacts may be exacerbated by the ongoing economic disruption caused by the COVID-19 global pandemic. Although we are based in the United Kingdom, we source research and development, manufacturing, consulting and other services from the United States and the European Union. Further, potential future revenue may be derived from abroad, particularly from the United States. As a result, our business and the price of our ADSs may be affected by fluctuations in foreign exchange rates not only between the pound sterling and the U.S. Dollar, but also the Euro, which may have a significant impact on our results of operations and cash flows from period to period. Currently, we do not have any exchange rate hedging arrangements in place.

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 experts named herein who are residents of the United Kingdom or countries other than the United States any judgments obtained in U.S. courts in civil and commercial matters, including judgments under the U.S. federal securities laws.

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 \$33.0 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 needed 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 usual and 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.

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, could severely disrupt our business. If a natural disaster occurred, we could be prevented from using 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, financial condition, results of operations and prospects.

The anticipated phasing out of LIBOR may adversely affect the value of any outstanding debt instruments.

National and international regulators and law enforcement agencies have conducted investigations into a number of rates or indices known as “reference rates.” Actions by such regulators and law enforcement agencies may result in changes to the manner in which certain reference rates are determined, their discontinuance, or the establishment of alternative reference rates. In particular, in July 2017, the Chief Executive of the UK Financial Conduct Authority, or FCA, which regulates LIBOR, announced that the FCA will no longer persuade or compel banks to submit rates for the calculation of LIBOR after 2021. This deadline was extended until June 2023 for a number of key U.S. dollar benchmark maturities.

At this time, it is not possible to predict the effect that these developments, any discontinuance, modification or other reforms to LIBOR or any other reference rate, or the establishment of alternative reference rates may have on LIBOR, other benchmarks, or LIBOR-based debt instruments. Uncertainty as to the nature of such potential discontinuance, modification, alternative reference rates or other reforms may materially adversely affect the trading market for securities linked to such benchmarks. Furthermore, the use of alternative reference rates or other reforms could cause the interest rate calculated for the LIBOR-based debt instruments to be materially different than expected.

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 litigations are often brought against companies following a decline in the market price of its 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 108 Cannon Street, London EC4N 6EU, United Kingdom. We lease approximately 14,000 square feet of office space at this location and our lease for this location extends through January 2023. We also lease approximately 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, 2021, 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

Our American Depositary Shares, or ADSs, each represent one ordinary share, nominal value £0.10 per share, of Orchard Therapeutics plc. 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 Global Select Market under the symbol "ORTX" since October 31, 2018. As of March 15, 2022, there were approximately 53 holders of record of our ordinary shares, nominal value £0.10 per share and one holder of record of our ADSs. The closing sale price per ADS on The Nasdaq Global Select Market on March 15, 2022 was \$0.71.

Sales of Unregistered Securities

On December 6, 2021, we issued 22,758 ordinary shares to Gene Therapy Consulting S.r.l. in connection with milestones that were deemed to have been met pursuant to a consulting agreement. The offer, sale, and issuance of the shares is exempt from registration pursuant to Section 4(a)(2) of the Securities Act of 1933, as amended, as a transaction by an issuer not involving a public offering.

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 deepest and 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, 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 focused on our transition 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 \$144.6 million for the year ended December 31, 2021. As of December 31, 2021, we had an accumulated deficit of \$750.2 million. As of December 31, 2021, we had cash, cash equivalents and marketable securities of \$220.1 million, excluding amounts held in escrow deposits. 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

On February 9, 2021, we 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 our 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 “Private Placement”). The Private Placement resulted in net proceeds to us of \$143.7 million after deducting placement agent fees of \$6.0 million and other offering-related costs of \$0.3 million. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement we entered into with the purchasers named therein on February 4, 2021. All non-voting ordinary shares have been converted to ordinary shares as of December 31, 2021.

The ADSs representing the ordinary shares issued in the Private Placement were registered for resale on an automatic shelf registration statement on Form S-3 filed with the SEC on April 8, 2021.

On May 28, 2021, we notified UCL Business Plc (“UCLB”) and The Regents of the University of California (“UCLA”) that we were terminating the license relating to our OTL-101 program for ADA-SCID, which was granted to us pursuant to the license agreement, dated February 6, 2016, among us, UCLB and UCLA, as amended (the “License Agreement”), such termination to be effective 30 days after the date of such notice. Except for the termination of such license, the License Agreement continues in full force and effect.

On July 1, 2021, the Company announced a strategic collaboration with 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.

Under the terms of the collaboration, Pharming has been 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 preclinical 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 \$17.5 million comprising \$10.0 million in cash and a \$7.5 million equity investment from Pharming at a premium to the Company’s then recent share price, resulting in the issuance of 1,227,738 ordinary shares subject to resale restrictions. 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.

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 our new strategic focus, we plan to reduce our workforce by approximately 30%. We expect to recognize employee-related termination costs related to the restructuring of approximately \$2.5 million during the first and second quarter of 2022. We also expect to incur discontinuation costs relating to OTL-102, OTL-103 and Strimvelis, such as contract termination fees and non-cancellable commitments. At the time of the filing of this Annual Report on Form 10-K, we are unable to determine the estimated discontinuation costs in good faith because such costs are subject to a number of variables that are not entirely within our control.

Business update regarding COVID-19

The current COVID-19 pandemic has presented substantial public health and economic challenges around the world and is affecting our employees, patients, communities and business operations, as well as the U.S. and global economies and financial markets. The impact of this pandemic has been and will likely continue to be extensive in many aspects of society and will likely continue to result in significant disruptions to the global economy, as well as businesses and capital markets around the world.

In an effort to halt the outbreak of COVID-19, a number of countries, including the United States, United Kingdom and Italy, have placed significant restrictions on travel. While some restrictions have been relaxed since the beginning of the pandemic, many restrictions are still in place. In the U.S. and UK, our office-based employees have been primarily working from home since March 2020. Limitations on travel and other social distancing measures may have an effect on our preclinical and clinical activities and regulatory timelines. While our clinical sites are still treating and following up with patients in clinical trials, these centers are also devoting significant resources to patients with COVID-19 and may need to devote additional resources as variants of COVID-19 lead to a potential rise in hospitalizations, which could limit their ability to enroll additional patients in ongoing clinical studies. While we believe we have enrolled and treated enough patients to support a first regulatory filing for OTL-200 in the U.S., COVID-19-related impacts shifted the enrollment timeline for our OTL-201 trial for the treatment of MPS-IIIa by three months.

As additional variants of the virus proliferate, potential renewed travel and stay-at-home orders could adversely affect our contract manufacturers and third-party logistics providers. To date, our third-party contract development and manufacturing organization (CDMO) partners have continued to operate at or near normal levels. While we currently do not anticipate any interruptions, it is possible that the COVID-19 pandemic and response efforts may have an impact in the future on our or our third-party suppliers' and CDMO partners' ability to manufacture our products in development. Any prolonged material disruptions to our employees, suppliers, CDMOs, vendors or patients could impact our operating results and could lead to impairments. To date, we have recorded impairments on long-lived assets that are due to a combination of a corporate restructuring and COVID-19 market impacts.

In addition, our ability to access the capital markets could be impacted if there are future disruptions to capital markets that result from the COVID-19 pandemic.

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 Sales

During the years ended December 31, 2021 and 2020, we recognized \$0.7 million and \$2.6 million revenue from sales of Strimvelis, respectively. Libmeldy received approval from the European Commission in December 2020 and, if we are able to identify patients and secure reimbursement for our treatment, we may begin to generate revenue from the sale of Libmeldy in Europe in early 2022. Strimvelis is distributed exclusively at the San Raffaele Hospital in Milan, Italy.

Collaboration revenue

During the year ended December 31, 2021, we recognized \$1.0 million 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. Under this method, revenue is recorded as a percentage of the estimated transaction price based on the extent of progress towards completion. Under this method, the impact of this adjustment 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.

Cost of product sales

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

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, preclinical 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 preclinical and clinical trials;
- expenses to acquire technologies to be used in research and development;
- salaries, benefits and other related costs, including share-based compensation expense, for personnel engaged in research and development functions;
- costs 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 preclinical study and clinical trial materials;
- costs related to compliance with regulatory requirements;
- facility-related expenses, which include direct depreciation costs and allocated expenses for rent and maintenance of facilities, 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 Stimpvelis loss provision is also recorded as an offset to research and development expense (see Note 2 of our consolidated financial statements).

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 preclinical and clinical development activities. License fees and other costs incurred after a product candidate has been designated and that are directly related to the product candidate are included in direct research and development expenses for that program. License fees and other costs incurred prior to designating a product candidate 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 remain consistent quarter over quarter for the near term as we continue to: (i) expedite the clinical development and seek to obtain marketing approval for our product candidates, including OTL-200 in the U.S. for MLD; (ii) work towards the clinical development of our early clinical phase product candidates, which may include initiating pivotal clinical trials for OTL-203 in MPS-IH and expanding the Phase I/II study for OTL-201 in MPS-III A; (iii) reduce our investment in and development expenses for OTL-300 for TDT and reallocate these financial resources to other programs; (iv) seek to improve the efficiency and scalability of our outsourced manufacturing processes and supply chain; (v) build process development and analytical capabilities in the near term, and potential manufacturing capabilities in the longer term; and (vi) continue to discover and develop additional product candidates. For example, in April 2020, we announced our intention to accelerate our research and development efforts for projects in less rare indications, including two new research programs in genetic subsets of frontotemporal dementia (FTD) and Crohn's disease, and in November 2020 we announced a new program in amyotrophic lateral sclerosis (ALS). We also expect to incur additional expenses related to milestone, royalty payments and maintenance fees payable to third parties with whom we have entered into license agreements to acquire the rights related to our product candidates.

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. The Amended Credit Facility bears a variable interest rate at a rate of 5.95% above LIBOR, plus a final payment equal to 3.5% of the principal borrowed under the Amended Credit Facility. LIBOR phases out in June 2023, at which point the Company and MidCap will agree on a new reference rate.

Other income (expense)

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

Results of operations

Information pertaining to fiscal year 2020 was included in our Annual Report on Form 10-K for the year ended December 31, 2020 on page 120 under Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," which was filed with the U.S. Securities and Exchange Commission on March 2, 2021.

Comparison of the years ended December 31, 2021 and 2020

The following table summarizes our results of operations for the years ended December 31, 2021 and 2020:

	Year Ended December 31,		Change
	2021	2020	
Product sales, net	\$ 700	\$ 2,595	\$ (1,895)
Collaboration revenue	975	—	975
Total revenues	\$ 1,675	\$ 2,595	\$ (920)
Costs and operating expenses			
Cost of product sales	226	857	(631)
Research and development	86,977	93,730	(6,753)
Selling, general and administrative	54,905	64,986	(10,081)
Total costs and operating expenses	142,108	159,573	(17,465)
Loss from operations	(140,433)	(156,978)	16,545
Other (expense) income:			
Interest income	412	3,185	(2,773)
Interest expense	(2,497)	(2,328)	(169)
Other (expense) income, net	(1,238)	3,411	(4,649)
Total other (expense) income, net	(3,323)	4,268	(7,591)
Net loss before income tax	(143,756)	(152,710)	8,954
Income tax (expense) benefit	(828)	731	(1,559)
Net loss attributable to ordinary shareholders	\$ (144,584)	\$ (151,979)	\$ 7,395

Research and development expenses

The table below summarizes our research and development expenses by therapeutic area:

	<u>Year Ended December 31,</u>		<u>Change</u>
	<u>2021</u>	<u>2020</u>	
	(in thousands)		
Direct research and development expenses by therapeutic area:			
Neurometabolic disorders	\$ 22,443	\$ 17,714	4,729
Primary immune deficiencies	17,801	21,073	(3,272)
Blood disorders	743	2,255	(1,512)
Other research and preclinical programs under development	5,636	3,479	2,157
Total direct research and development expenses	46,623	44,521	2,102
Research and discovery and unallocated costs			
Personnel related (excluding share-based compensation)	32,421	35,949	(3,528)
Share-based compensation	9,214	11,679	(2,465)
Accretion of Strimvelis loss provision	(1,037)	(2,413)	1,376
Research and development tax credit	(13,920)	(21,130)	7,210
Impairment of long-lived assets	—	5,650	(5,650)
Facility and other	13,676	19,474	(5,798)
Total indirect research and development expenses	40,354	49,209	(8,855)
Total research and development expenses	\$ 86,977	\$ 93,730	(6,753)

Direct research and development expenses for neurometabolic programs increased by \$4.7 million. The increase is primarily driven by a \$3.3 million increase in OTL-203 for MPS-I, and a \$2.3 million increase for OTL-200 for MLD/Libmeldy, offset by a \$0.9 million decline in OTL-201 for MPS-IIIa.

Direct research and development expenses for primary immune deficiencies declined by \$3.3 million. The decline is primarily driven by a \$3.8 million decline in OTL-101 for ADA-SCID, and a \$1.9 million decline in OTL-102 for X-CGD, offset by a \$1.8 million increase in OTL-103 for WAS, and \$0.6 million increase in Strimvelis. The primary decline in primary immune deficiencies was for OTL-101, and is due to the termination of the license for this program with UCLA/UCLB.

Direct research and development expenses for our blood disorder programs declined by \$1.5 million, as a result of incurring lower expenses for OTL-300 for TDT following our reduction in investment in that product candidate in connection with our strategic reprioritization in 2020. The decrease in expenses was due to a decline in manufacturing expenses.

Direct expenses associated with other research and preclinical programs increased by \$2.2 million. This was primarily due to increased costs for preclinical programs in hereditary angioedema (HAE), frontotemporal dementia with progranulin mutations (GRN-FTD) and Crohn's disease with mutations in the nucleotide-binding oligomerization domain-containing protein 2 (NOD2-CD), as well as other undisclosed discovery programs.

Unallocated research and development costs and offsets to research and development expenses declined by \$8.9 million. This was primarily due to a decline in personnel related costs of \$3.6 million and share-based compensation of \$2.5 million. The decline in personnel costs is due to \$3.6 million in severance associated with the consolidation and closure of our research and development and manufacturing facilities in California in 2020, which did not recur in 2021, as well as lower compensation costs. We also took a \$5.7 million non-cash asset impairment charge associated with assets at our former California research facilities in 2020 that did not recur in 2021. Other facility, travel, and unallocated platform-related research and development costs have declined by \$5.7 million.

Research and development expenses were further offset by \$13.9 million as a result of the benefits of the UK research and development tax credit that is recorded as an offset to research and development expense. Tax credit benefits decreased by \$7.2 million primarily due expenses qualifying for credit under a less favorable credit regime as a result of EU State Aid Cap thresholds being met for certain programs. Accretion of the Strimvelis loss provision, which is also accounted for as an offset to research and development expense, declined by \$1.4 million as we have adjusted our ongoing estimate due to our

reduction of investment in OTL-101 and have extended out the expected period of losses for Strimvelis, which results in lower amortization of the loss provision in a given period.

Selling, general and administrative expenses

The table below summarizes our selling, general and administrative expenses by functional area:

	<u>Year Ended December 31,</u>		<u>Change</u>
	<u>2021</u>	<u>2020</u>	
	(in thousands)		
Selling, general and administrative expenses:			
Personnel (excluding share-based compensation)	\$ 18,711	\$ 22,890	(4,179)
Share-based compensation	13,322	16,283	(2,961)
Consulting, professional, and insurance-related costs	12,679	11,315	1,364
Marketing, promotions, and advocacy	5,259	8,093	(2,834)
Facilities and IT-related costs	4,539	5,422	(883)
Other	395	983	(588)
Total selling, general, and administrative expenses:	\$ 54,905	\$ 64,986	\$ (10,081)

Selling, general and administrative expenses were \$54.9 million in 2021, compared to \$65.0 million in 2020. The decline of \$10.1 million was primarily due to lower personnel and share-based compensation. Personnel costs declined by \$4.2 million, generally due to \$1.3 million in severance charges associated with our corporate restructuring and CEO transition 2020 that did not recur in 2021, and a decline in salary and bonus charges associated with our selling, general, and administrative staff. Share-based compensation expense declined by \$3.0 million in 2021 compared to 2020 due to a \$2.7 million charge associated with the modification of our former CEO's share options in 2020 that did not recur in 2021. Consulting, professional, and insurance-related costs increased by of \$1.4 million primarily due to an increase in directors' and officers' insurance. Expenses associated with marketing and commercialization of Strimvelis, and costs associated with preparing for the potential future commercialization of our product candidates, if approved, declined by \$2.8 million. Facilities and IT costs and other expenses also declined, as we have realized savings from our 2020 corporate restructuring.

Other (expense) income, net

Other (expense) income, net for 2021 and 2020 was a loss of \$3.3 million and a gain of \$4.3 million, respectively. During 2021, we had realized and unrealized losses on foreign currency transactions of \$1.2 million, compared to \$3.4 million in gains for 2020. These gains and losses are primarily due to fluctuations in the exchange rate between British Pound and U.S. Dollars as it relates to our foreign currency denominated monetary assets and liabilities. Interest income declined by \$2.8 million due to lower investment portfolio balances as a result of cash used for operations.

Liquidity and capital resources

From our inception through December 31, 2021, 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 preclinical and clinical development. In December 2020, the European Commission granted standard marketing authorization for Libmeldy. We expect to launch Libmeldy in Europe and generate product sales in early 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, proceeds 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., and our Original Credit Facility and our Amended Credit Facility.

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. As of December 31, 2021, we have not sold any shares under the Sales Agreement. 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.

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.

Cash flows

Information pertaining to fiscal year 2020 was included in the Company's Annual Report on Form 10-K for the year ended December 31, 2020 beginning on page 120 under Item 7, "Management's Discussion and Analysis of Financial Condition and Results of Operations," which was filed with the U.S. Securities and Exchange Commission on March 2, 2021.

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

	For the Year Ended December 31,	
	2021	2020
	(in thousands)	
Net cash used in operating activities	\$ (125,097)	\$ (126,274)
Net cash from investing activities	(32,165)	157,379
Net cash provided by financing activities	158,066	3,936
Effect of exchange rate changes on cash	(27)	1,043
Net increase in cash, cash equivalents, and restricted cash	<u>\$ 777</u>	<u>\$ 36,084</u>

Operating activities

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.

During 2020, operating activities used \$126.3 million of cash, primarily resulting from our net loss of \$152.0 million. Cash usage from changes in our operating assets and liabilities was \$3.6 million. There was an \$11.7 million increase from our UK research and development tax credit receivable, for which we received \$33.8 million during 2020 (which was associated with our 2018 and 2019 tax credit claims), offset by \$21.1 million taken as an offset to research and development expense that will be included in our 2020 claim. Further, payment of accruals and accounts payable resulted in cash outflows of \$12.3 million. The decline in these accounts is primarily due to timing of payments in comparison with the prior year-end. Non-cash adjustments to operating activities of \$29.3 million was primarily due to \$28.0 million in non-cash share-based compensation expense, offset by \$2.4 million in amortization of the Strimvelis loss provision as an offset to research and development expense. Additionally, we took \$5.7 million in asset impairments associated with our restructuring. There were also unrealized foreign currency transaction gains on investments, intercompany accounts, and foreign-currency denominated payables and receivables held by our UK subsidiary of \$3.9 million. Finally, we had \$2.3 million in deferred income tax benefits during 2020.

Investing activities

During 2021 and 2020, we used \$32.2 million and generated \$157.4 million, respectively, of cash in investing activities. The change in cash from investing activity is primarily due to proceeds from sales and maturities of marketable debt securities that we utilize for operating activities. Further, in 2020 we made \$10 million construction deposit associated with our Fremont lease, and we received \$1.9 million in receipts from the escrow account, as compared to receiving \$0.2 million in 2021.

Financing activities

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.

During 2020, we received proceeds of \$3.9 million from the exercise of share options and the issuance of ordinary shares as part of our 2018 Employee Share Purchase Plan, or 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 preclinical activities and clinical trials of our product candidates and as we:

- seek marketing approvals for our product candidates that successfully complete clinical trials, if any;
- continue to grow a sales, marketing and distribution infrastructure for our commercialization of 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 preclinical programs;
- initiate additional clinical trials and preclinical studies for our other product candidates;
- seek to identify and develop, acquire or in-license additional product candidates;
- develop the necessary processes, controls and manufacturing data to obtain marketing approval for our product candidates, 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 if we are able to generate product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

We believe our existing cash will enable us to fund our operating expenses and capital expenditure requirements into 2024. 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, 2021 and 2020.

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.

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

Valuation of share-based compensation

We measure share-based awards granted to employees, non-employees and directors based on the fair value on the date of the grant and recognize compensation expense for those awards over the requisite service period, which is generally the vesting period of the respective award. Forfeitures are accounted for as they occur. Generally, we issue share-based awards 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.

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, 2021, we had cash, cash equivalents, marketable securities, and restricted cash of \$224.4 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, 2021, the carrying value of the term loans under the credit facility was \$32.9 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. The discontinuation of LIBOR will require these arrangements to be modified in order to replace LIBOR with an alternative reference interest rate, which could impact our cost of funds. Our credit facilities include a provision for the determination of a successor LIBOR rate.

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 \$1.2 million and gains of \$3.4 million for the years ended December 31, 2021 and 2020. 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, 2021, 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, 2021.

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, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

Costs Associated with Exit or Disposal Activities

On March 25, 2022, we approved a restructuring, pursuant to which the Company proposed to reduce its workforce by approximately 30%. The workforce reduction is subject to a consultation process with certain employees in the United Kingdom. The proposed reduction in force is expected to take place during, and be substantially completed by, the end of the second quarter 2022. 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.

The restructuring is expected to extend our cash runway into 2024. As part of the restructuring, we expect to recognize employee-related termination costs of approximately \$2.5 million during the first and second quarters of 2022. We also expect to incur discontinuation costs relating to OTL-102, OTL-103 and Strimvelis, such as contract termination fees and non-cancellable commitments. At the time of the filing of this Annual Report on Form 10-K, we are unable to make a determination of the discontinuation costs in good faith because such costs are subject to a number of variables that are not entirely within the Company’s control. These estimates of the expenses that the Company expects to incur and potential cost savings in connection with the proposed restructuring, and the timing thereof, are subject to a number of assumptions and actual results may differ. The Company may also incur additional costs not currently contemplated due to events that may occur as a result of, or that are associated with, the restructuring.

“At the Market” Equity Offering Program

As previously disclosed, in February 2020 we entered into a sales agreement (the “Sales Agreement”) with Cowen and Company, LLC (“Cowen”), pursuant to which we had the ability to issue and sell, from time to time at our option, ADSs

representing our ordinary shares having an aggregate offering price of up to \$100 million, through an “at the market” equity offering program under which Cowen acted as sales agent. 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. We are not subject to any termination penalties related to the termination of the Sales Agreement. 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. A copy of the Sales Agreement was filed as Exhibit 1.2 to the post-effective amendment to our Registration Statement on Form S-3, filed with the SEC on February 27, 2020 (the “Form S-3”). The description of the Sales Agreement contained in this Annual Report does not purport to be complete and is qualified in its entirety by reference to the copy of the Sales Agreement filed as Exhibit 1.2 to the Form S-3.

Frank Thomas Transitional Services Agreement

On March 30, 2022, the Company and Frank Thomas entered into an amendment (the “Amendment”) to his Transitional Services Agreement, dated November 3, 2021 (as amended by the Amendment, the “Agreement”). Pursuant to the Amendment, Mr. Thomas will continue to serve as President and Chief Operating Officer of the Company and provide services for the Company on a full-time basis until December 31, 2022, unless his employment ends earlier or the Company and Mr. Thomas agree to an extension (such period, the “Transition Period”). During the Transition Period, the Amendment provides, among other things, that in exchange for entering into and complying with the Agreement, which includes a customary release of claims, Mr. Thomas will (i) continue to receive his base salary, subject to an increase in the base salary rate in an amount determined by the Board of Directors of the Company (or the Compensation Committee thereof) to be effective at the time that other executive team members of the Company receive base salary rate increases, (ii) remain eligible to participate in the Company’s group employee benefit plans, (iii) continue to vest in his stock options, and (iv) subject to the approval of the Company’s Board of Directors (or the Compensation Committee thereof), receive an award of stock options to purchase shares of the Company and/or other form of equity. Further, if Mr. Thomas remains employed by the Company on October 1, 2022, or in the event that he is terminated without “Cause” (as defined in the Agreement) prior to October 1, 2022 but has, among other things, executed an updated release of claims, then Mr. Thomas will be eligible to receive a cash incentive compensation in an amount equal to 25% of Mr. Thomas’ then current base salary, to be paid no later than October 31, 2022. In addition, at the conclusion of his employment with the Company, provided that, among other things, Mr. Thomas’ employment is not terminated by the Company for “Cause” and subject to the execution and effectiveness of an updated release, Mr. Thomas will be entitled to the following benefits (a) for up to six months, the Company shall pay the monthly employer COBRA premium for the same level of group health coverage as in effect at the conclusion of Mr. Thomas’ employment, (b) be eligible to receive a cash incentive compensation in an amount equal to 25% of Mr. Thomas’ then current base salary, to be paid at the time that the Company pays its executives their annual incentive compensation for 2022, which will be no later than March 15, 2023, and (c) subject to approval by the Company’s Board of Directors (or the Compensation Committee thereof) (x) continued vesting of all equity awards until April 1, 2023 and (y) an extension of the exercise period with respect to the vested shares of his stock options as of the date that the Company receives Mr. Thomas’ executed updated release of claims, until the earlier of (A) April 1, 2024 or (B) the expiration date of the applicable share option.

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).

We do not believe that we were a PFIC in the 2021 taxable year, though we have not made a determination regarding our PFIC status in the current taxable year. However, a separate determination must be made after the close of each taxable year as to whether we are a PFIC for that year. As a result, our PFIC status may change from year to year, and we may be classified as a PFIC currently or in the future. The total value of our assets for purposes of the asset test generally will be calculated using the market price of the ordinary shares or ADSs, which may fluctuate considerably. Fluctuations in the market price of the ordinary shares or ADSs may result in our being a PFIC for any taxable year. However, if we are a “controlled foreign corporation” for any taxable year (see discussion below in “Controlled foreign corporation considerations”), the value of our assets for purposes of the asset test will be determined based on the tax basis of such assets which could increase the likelihood that we are treated as a PFIC. Because of the uncertainties involved in establishing our PFIC status, there can be no assurance regarding if we currently are treated as a PFIC or may be treated as a PFIC in the future.

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

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

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

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

If we determine that we are a PFIC for any taxable year, we currently expect that we would provide the information

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

U.S. Holders can avoid the interest charge on excess distributions or gain relating to the ordinary shares or ADSs by making a mark-to-market election with respect to the ordinary shares or ADSs, provided that the ordinary shares or ADSs are “marketable.” Ordinary shares or ADSs will be marketable if they are “regularly traded” on certain U.S. stock exchanges or on a foreign stock exchange that meets certain conditions. For these purposes, the ordinary shares or ADSs will be considered regularly traded during any calendar year during which they are traded, other than in de minimis quantities, on at least 15 days during each calendar quarter. Any trades that have as their principal purpose meeting this requirement will be disregarded. Our ADSs will be listed on Nasdaq, which is a qualified exchange for these purposes. Consequently, if our ADSs remain listed on Nasdaq and are regularly traded, we expect the mark-to-market election would be available to U.S. Holders if we are a PFIC. Each U.S. Holder should consult its tax advisor as to the whether a mark-to-market election is available or advisable with respect to the ordinary shares or ADSs.

A U.S. Holder that makes a mark-to-market election must include in ordinary income for each year an amount equal to the excess, if any, of the fair market value of the ordinary shares or ADSs at the close of the taxable year over the U.S. Holder’s adjusted tax basis in the ordinary shares or ADSs. An electing holder may also claim an ordinary loss deduction for the excess, if any, of the U.S. Holder’s adjusted basis in the ordinary shares or ADSs over the fair market value of the ordinary shares or ADSs at the close of the taxable year, but this deduction is allowable only to the extent of any net mark-to-market gains for prior years. Gains from an actual sale or other disposition of the ordinary shares or ADSs will be treated as ordinary income, and any losses incurred on a sale or other disposition of the shares will be treated as an ordinary loss to the extent of any net mark-to-market gains for prior years. Once made, the election cannot be revoked without the consent of the Internal Revenue Service, or the IRS, unless the ordinary shares or ADSs cease to be marketable.

However, a mark-to-market election generally cannot be made for equity interests in any lower-tier PFICs that we own, unless shares of such lower-tier PFIC are themselves “marketable.” As a result, even if a U.S. Holder validly makes a mark-to-market election with respect to our ordinary shares or ADSs, the U.S. Holder may continue to be subject to the PFIC rules (described above) with respect to its indirect interest in any of our investments that are treated as an equity interest in a PFIC for U.S. federal income tax purposes. U.S. Holders should consult their tax advisors to determine whether any of these elections would be available and if so, what the consequences of the alternative treatments would be in their particular circumstances.

Unless otherwise provided by the U.S. Treasury, each U.S. shareholder of a PFIC is required to file an Annual Report containing such information as the U.S. Treasury may require. A U.S. Holder’s failure to file the Annual Report will cause the statute of limitations for such U.S. Holder’s U.S. federal income tax return to remain open with regard to the items required to be included in such report until three years after the U.S. Holder files the Annual Report, and, unless such failure is due to reasonable cause and not willful neglect, the statute of limitations for the U.S. Holder’s entire U.S. federal income tax return will remain open during such period. U.S. Holders should consult their tax advisors regarding the requirements of filing such information returns under these rules.

WE STRONGLY URGE 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 2020/2021 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 7.5% to the extent the excess amount falls within the basic rate band, 32.5% to the extent the excess amount falls within the higher rate band, and 38.1% to the extent the excess amount falls within the additional rate band.

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 2020/2021).

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 2020/2021). 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 2020/2021), 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 2020/2021).

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 (currently 19% for the tax year 2020/2021) would apply.

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 cancelled or, if already paid, repaid (generally with interest), where a transfer instrument has been duly stamped within six years of the charge arising, (either by paying the stamp duty or by claiming an appropriate relief) or if the instrument is otherwise exempt from stamp duty.

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 2022 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 2022 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 2022 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 2022 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 2022 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:

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(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, by and among the registrant, Glaxo Group Limited and GlaxoSmithKline Intellectual Property Development Ltd., dated April 11, 2018 (Schedules, exhibits, and similar supporting attachments are omitted pursuant to Item 601(b)(2) of Regulation S-K. The registrant agrees to furnish a supplemental copy of any omitted schedule or similar attachment to the Securities and Exchange Commission upon request).	Form F-1	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	Form of American Depositary Receipt (included in Exhibit 4.1)	Form 20-F	2.2	Mar. 22, 2019	001-38722
4.3	Investment and shareholders' agreement by and between the registrant and the shareholders named therein, dated August 2, 2018, as amended.	Form F-1	10.1	Jun. 3, 2019	333-231916
4.4	Description of the registrant's securities.	Form 10-K	4.4	Feb. 27, 2020	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, by and among the registrant, Glaxo Group Limited, GlaxoSmithKline Intellectual Property Development Limited, GlaxoSmithKline S.p.A., Fondazione Telethon and Ospedale San Raffaele (in its own capacity and as successor in interest to Fondazione Centro San Raffaele Del Monte Tabor), dated April 5, 2018.	Form F-1	10.4	Oct. 4, 2018	333-227698
10.9	Research and Development Collaboration and License Agreement, by and among Glaxo Group Limited, Fondazione Telethon and Fondazione Centro San Raffaele del Monte Tabor, dated October 15, 2010, as amended.	Form F-1	10.5	Oct. 4, 2018	333-227698
10.10	Securities Purchase Agreement dated February 4, 2021, by and among Orchard Therapeutics plc and the Purchasers named therein	Form 10-Q	10.1	May 13, 2021	001-38722
10.11	Lease Agreement, dated as of January 19, 2018, by and between the Registrant and New Connect Investments Limited.	Form F-1	10.7	Oct. 4, 2018	333-227698
10.12††	Lease Agreement, dated as of December 11, 2018, by and between BPP Pacific Industrial CA Non-REIT Owner 2 LLC and Orchard Therapeutics North America.	Form 20-F/A	4.12	Apr. 26, 2019	001-38722
10.13†	License and Development Agreement, by and between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016, as amended.	Form F-1	10.8	Oct. 4, 2018	333-227698
10.14††	Amendment Nos. 5 and 6 to License and Development Agreement, by and between the registrant and Oxford BioMedica (UK) Limited, dated November 28, 2016.	Form 10-Q	10.2	May 7, 2020	001-38722
10.15	Senior Term Facilities Agreement, dated May 24, 2019, as amended and restated on May 28, 2021, among Orchard Therapeutics plc, the entities listed as original guarantors therein, MidCap Financial (Ireland) Limited, and the additional lenders party thereto from time to time.	Form 10-Q	10.1	Aug. 4, 2021	001-38722

10.16#	Employment Agreement between the registrant, Orchard Therapeutics North America, and Frank Thomas, effective September 1, 2019.	Form 10-K	10.15	Feb. 27, 2020	001-38722
10.17#	First Amendment to Employment Agreement, dated March 18, 2020, by and among the Company, Orchard Therapeutics North America and Frank Thomas.	Form 8-K	10.4	Mar. 20, 2020	001-38722
10.18#	Transitional Services Agreement, dated November 3, 2021, between the Company, Orchard Therapeutics North America and Frank Thomas.	Form 10-Q	10.1	Nov. 4, 2021	001-38722
10.19*#	Amendment to the Transitional Services Agreement, dated March 30, 2022, between the Company, Orchard Therapeutics North America and Frank Thomas.				
10.20#	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
10.21#	Variation to Contract of Employment, dated March 18, 2020, by and between Orchard Therapeutics (Europe) Limited and Hubert Gaspar, M.D., Ph.D.	Form 8-K	10.3	Mar. 20, 2020	001-38722
10.22††	Manufacturing and Technology Development Master Agreement, by and between Orchard Therapeutics (Europe) Limited, a wholly-owned subsidiary of the registrant, and MolMed S.p.A., dated July 2, 2020.	Form 10-Q	10.1	Aug. 6, 2020	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				

- 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 (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101).

* 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 30, 2022

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 resubstitution 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.

<u>Signature</u>	<u>Title</u>	<u>Date</u>
<u>/s/ Bobby Gaspar</u> Bobby Gaspar	Chief Executive Officer and Director (Principal Executive Officer)	March 30, 2022
<u>/s/ Frank E. Thomas</u> Frank E. Thomas	President and Chief Operating Officer (Principal Financial Officer and Principal Accounting Officer)	March 30, 2022
<u>/s/ James A. Geraghty</u> James A. Geraghty	Chairman of the Board of Directors	March 30, 2022
<u>/s/ Steven M. Altschuler</u> Steven M. Altschuler, M.D.	Director	March 30, 2022
<u>/s/ Joanne T. Beck</u> Joanne T. Beck, Ph.D.	Director	March 30, 2022
<u>/s/ John Curnutte</u> John Curnutte, M.D., Ph.D.	Director	March 30, 2022
<u>/s/ Marc Dunoyer</u> Marc Dunoyer	Director	March 30, 2022
<u>/s/ Charles A. Rowland, Jr.</u> Charles A. Rowland, Jr.	Director	March 30, 2022
<u>/s/ Alicia Secor</u> Alicia Secor	Director	March 30, 2022

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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, 2021 and 2020, 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, 2021 and 2020, 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 audits 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.

United Kingdom (U.K.) Research and Development Tax Credits

As described in Note 2 to the consolidated financial statements, the Company carries out research and development activities and is able to submit tax credit claims under two U.K. 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. Each reporting period, management evaluates the tax relief programs the Company is expected to be eligible for and records a reduction to research and development expense for the portion of the expense that it expects to qualify under the programs, that it plans to submit a claim for, and it has reasonable assurance that the amount will ultimately be realized. Management assesses its 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 U.K. government, which are subject to interpretation. For the year ended December 31, 2021, the Company recorded \$13.9 million

as a reduction of research and development expense related to these programs and has a related tax credit receivable of \$30.7 million as of December 31, 2021.

The principal considerations for our determination that performing procedures relating to the U.K. research and development tax credits is a critical audit matter are (i) the significant judgment by management when determining the nature and amount of expenses that qualify under the tax relief programs and estimating the amount of tax credit claims that will ultimately be realized based on the criteria established by the U.K. government; (ii) a high degree of auditor judgment, subjectivity, and effort in performing procedures and evaluating audit evidence relating to the U.K. research and development tax credits; and (iii) the audit effort involved the use of professionals with specialized skill and knowledge.

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 determining the programs the Company expects to qualify for and file tax credit claims under and the total qualifying expenses claimed or to be claimed, (ii) evaluating the reasonableness of management's assessment of the amount expected to be realized considering the relevant criteria outlined in the tax relief programs, and (iii) testing the completeness and accuracy of the data underlying the tax credit calculations. Professionals with specialized skill and knowledge were used to assist in evaluating management's assessment of the U.K. research and development tax relief programs the Company expects to qualify for and file tax credit claims under, testing management's research and development tax credit calculations, and evaluating the reasonableness of management's assessment of the amount expected to be realized.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 30, 2022

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,	
	2021	2020
Assets		
Current assets:		
Cash and cash equivalents	\$ 55,912	\$ 55,135
Marketable securities	164,195	136,813
Accounts receivable	1,480	878
Prepaid expenses and other current assets	23,011	13,365
Research and development tax credit receivable	30,723	17,344
Total current assets	<u>275,321</u>	<u>223,535</u>
Non-current assets:		
Operating lease right-of-use-assets	24,316	29,815
Property and equipment, net	4,767	4,781
Restricted cash	4,266	4,266
Intangible assets, net	4,149	3,076
Other assets	9,590	15,464
Total non-current assets	<u>47,088</u>	<u>57,402</u>
Total assets	<u>\$ 322,409</u>	<u>\$ 280,937</u>
Liabilities and shareholders' equity		
Current liabilities:		
Accounts payable	\$ 10,008	\$ 8,823
Accrued expenses and other current liabilities	24,318	28,943
Deferred revenue	346	—
Operating lease liabilities	7,335	8,934
Notes payable, current	786	4,861
Total current liabilities	<u>42,793</u>	<u>51,561</u>
Notes payable, long-term	32,086	20,204
Deferred revenue, net of current portion	12,519	—
Operating lease liabilities, net of current portion	19,278	24,168
Other long-term liabilities	5,783	6,570
Total liabilities	<u>112,459</u>	<u>102,503</u>
Commitments and contingencies (Note 18)		
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, 2021 and 2020, respectively; 125,674,095 and 98,283,603 shares issued and outstanding at December 31, 2021 and 2020, respectively.	16,253	12,507
Additional paid-in capital	940,675	771,194
Accumulated other comprehensive income	3,246	373
Accumulated deficit	(750,224)	(605,640)
Total shareholders' equity	<u>209,950</u>	<u>178,434</u>
Total liabilities and shareholders' equity	<u>\$ 322,409</u>	<u>\$ 280,937</u>

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,	
	2021	2020
Product sales, net	\$ 700	\$ 2,595
Collaboration revenue	975	—
Total revenues	1,675	2,595
Costs and operating expenses		
Cost of product sales	226	857
Research and development	86,977	93,730
Selling, general and administrative	54,905	64,986
Total costs and operating expenses	142,108	159,573
Loss from operations	(140,433)	(156,978)
Other (expense) income:		
Interest income	412	3,185
Interest expense	(2,497)	(2,328)
Other (expense) income, net	(1,238)	3,411
Total other (expense) income, net	(3,323)	4,268
Net loss before income tax	(143,756)	(152,710)
Income tax (expense) benefit	(828)	731
Net loss attributable to ordinary shareholders	\$ (144,584)	\$ (151,979)
Net loss per share attributable to ordinary shareholders, basic and diluted	\$ (1.17)	\$ (1.53)
Weighted average number of ordinary shares outstanding, basic and diluted	123,963,762	99,445,874
Other comprehensive income (loss)		
Foreign currency translation adjustment	3,124	(1,485)
Unrealized loss on marketable debt securities	(251)	(184)
Total other comprehensive income (loss)	2,873	(1,669)
Total comprehensive loss	\$ (141,711)	\$ (153,648)

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		Additional paid-in capital	Accumulated other comprehensive income (loss)	Accumulated deficit	Total
	Shares	Amount				
Balance at December 31, 2019	96,923,729	\$ 12,331	\$ 738,481	\$ 2,042	\$ (453,661)	\$ 299,193
Share-based compensation expense	—	—	27,962	—	—	27,962
Exercise of share options	1,154,441	149	3,316	—	—	3,465
Issuance of ESPP shares	107,262	14	657	—	—	671
Ordinary shares issued as part of consulting agreement	22,758	3	(3)	—	—	—
Ordinary shares issued as part of license agreement	75,413	10	781	—	—	791
Foreign currency translation	—	—	—	(1,485)	—	(1,485)
Unrealized gain on marketable debt securities	—	—	—	(184)	—	(184)
Net loss	—	—	—	—	(151,979)	(151,979)
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

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,	
	2021	2020
Cash flows from operating activities		
Net loss attributable to ordinary shareholders	\$ (144,584)	\$ (151,979)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	2,327	2,004
Share-based compensation	22,536	27,962
Impairment of long-lived assets	—	5,650
Non-cash interest expense	392	500
Amortization of provision on loss contract	(1,037)	(2,413)
Non-cash consideration for licenses and milestones	—	791
Deferred income taxes	1,131	(2,257)
Amortization of premium on marketable securities	1,514	770
Unrealized foreign currency and other non-cash adjustments	9,687	(3,674)
Changes in operating assets and liabilities:		
Accounts receivable	(624)	582
Research and development tax credit receivable	(13,920)	11,674
Prepaid expenses, other current assets, and other assets	(5,209)	(5,070)
Operating leases, right-of-use-assets	5,938	5,863
Accounts payable, accrued expenses, and other current liabilities	(9,452)	(12,278)
Deferred revenue	13,122	—
Other long-term liabilities	34	2,570
Operating lease liabilities	(6,952)	(6,969)
Net cash used in operating activities	\$ (125,097)	\$ (126,274)
Cash flows from investing activities		
Proceeds from sales and maturities of marketable securities	234,732	281,433
Purchases of marketable securities	(263,878)	(113,262)
Payment of construction deposit	—	(10,000)
Receipt of funds from construction deposit	216	1,876
Payments on intangible assets	(887)	—
Purchases of property and equipment	(2,348)	(2,668)
Net cash (used in) provided by investing activities	\$ (32,165)	\$ 157,379
Cash flows from financing activities		
Proceeds from modification of credit facility, net of debt issuance costs paid	7,375	—
Proceeds from employee equity plans	3,303	3,936
Payment of taxes on restricted stock vesting	(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	(6,355)	—
Net cash provided by financing activities	\$ 158,066	\$ 3,936
Effect of exchange rate changes on cash	(27)	1,043
Net increase in cash, cash equivalents and restricted cash	\$ 777	\$ 36,084
Cash, cash equivalents, and restricted cash —beginning of year	59,401	23,317
Cash, cash equivalents, and restricted cash —end of year	\$ 60,178	\$ 59,401
Supplemental disclosure of non-cash investing and financing activities		
Intangible assets and property and equipment in accounts payable and accrued expenses	2,589	3,096
Shares issued in consideration of license agreements	—	791
Employee equity plan proceeds received after year-end	—	200
Supplemental disclosure of cash flow information		
Lease assets obtained in exchange for new operating lease liabilities	552	17,486
Cash paid for interest	2,103	1,828
Cash paid for taxes	1,651	1,007

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

Orchard Therapeutics plc
Notes to Consolidated Financial Statements

1. Nature of Business and Basis of Presentation

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’s gene therapy product candidate 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.

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”) and has been listed on the Nasdaq Global Select Market since October 31, 2018. The Company’s ADSs each represent one ordinary share of the Company.

In December 2020, the Company received standard marketing authorization from the European Commission for Libmeldy™ (atidarsagene autotemcel), 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 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 “Private Placement”). The 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. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement entered into between the Company and the purchasers named therein on February 4, 2021. At December 31, 2021, all outstanding non-voting shares have been converted to voting ordinary shares.

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 quarantines, border closures, increased border controls, travel restrictions, shelter-in-place orders and shutdowns, business closures, cancellations of public gatherings and other measures.

The accompanying consolidated financial statements have been prepared on the basis of continuity of operations, realization of assets and the satisfaction of liabilities and commitments in the ordinary course of business. Through December 31, 2021, the Company funded its operations primarily with proceeds from the sale of convertible preferred shares, and ADSs in the IPO and follow-on offering. The Company has incurred recurring losses since its inception, including net losses of \$144.6 million and \$152.0 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, the Company had an accumulated deficit of \$750.2 million. The Company 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, 2021 of \$220.1 million will be sufficient to fund its operations and capital expenditure requirements for at least the next twelve months. 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 the Company 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.

Basis of presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (“U.S. GAAP”) and include the accounts of the Company and its wholly owned subsidiaries, after elimination of all intercompany accounts and transactions.

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.

2. Summary of Significant Accounting Policies

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 U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenue and expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual for research and development expenses, the research and development tax credit receivable, share-based compensation, collaboration agreement milestones, 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

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 maintains deposits in accredited financial institutions in excess of federally insured limits. The Company deposits its cash in financial institutions that it believes have high credit quality and has not experienced any losses on such accounts and does not believe it is exposed to any unusual credit risk beyond the normal credit risk associated with commercial banking relationships or entities for which it has a receivable.

Foreign currency

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. 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 \$1.2 million, and gains of \$3.4 million for the years ended December 31, 2021, and 2020, 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, results of the Company's operations are reported on a consolidated basis for 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 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 property and equipment of \$3.7 million and \$1.1 million located in the United Kingdom and United States, respectively, as of December 31, 2020. 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. The Company had right-of-use assets in the United States and United Kingdom and European Union of \$14.2 million and \$15.6 million, respectively, as of December 31, 2020.

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 at 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; 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 operation.

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 our consolidated balance sheet. 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 at December 31, 2021 and 2020. 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 at December 31, 2021 and 2020.

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:

	As of December 31,	
	2021	2020
Cash and cash equivalents	\$ 55,912	\$ 55,135
Restricted cash	4,266	4,266
Total cash, cash equivalents and restricted cash shown in the statement of cash flows	\$ 60,178	\$ 59,401

The Company also has \$7.9 million in an escrow account associated with the construction of the Company’s leased facility in Fremont, California, which the Company has ceased construction and build-out, and has subleased the facility to a third-party who intends to perform construction and build-out of the facility. Subject to the terms of the lease and reduction provisions, this escrow amount may be decreased to nil over time upon qualifying construction expenditures, or will be returned in late 2022 to the extent funds are not used. The Company deposited \$10.0 million into the account in the first quarter of 2020 and has received \$2.1 million in receipts from the escrow funds for work performed to date. Of the \$7.9 million remaining in the escrow account, the entire balance is classified within other prepaid expenses and other current assets on the consolidated balance sheets based on the timing of when the Company expects to receive the cash from the escrow agent.

Inventory

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 and the amount was not significant as of December 31, 2021.

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. In connection with the acquisition of Strimvelis in April 2018, and with the EMA approval of Libmeldy in December 2020, the Company subsequently began capitalizing inventory manufactured or purchased after these dates.

Intangible assets, net

Intangible assets, net consist 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.

Property and equipment:	Estimated useful life
Lab equipment	5-10 years
Leasehold improvements	Shorter of lease term or estimated useful life
Furniture and fixtures	4 years
Office and computer equipment	3-5 years

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 may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or

economic trends and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset group for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset group to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset group are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset group over its fair value, as determined in accordance with the related accounting literature.

Research and development costs

Research and development costs are expensed as incurred. Research and development expenses consist of costs incurred in performing research and development activities, including salaries, share-based compensation and benefits, facilities costs, depreciation, third-party license fees, certain milestone payments, and external costs of outside vendors engaged to conduct clinical development activities and clinical trials, the purchase of in-process research and development assets, as well as costs 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 or the related services are performed, or until it is no longer expected that the goods will be delivered, or the services rendered. In addition, funding from research grants is recognized as an offset to research and development expense on the basis of costs incurred on the research program. Royalties to third parties associated with our research grants will be accrued when they become probable.

Research contract costs and accruals

The Company has entered into various research and development 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 as of period end 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 companies 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 share-based awards granted to employees, consultants and directors based on the fair value of the shares and options on the date of the grant and recognizes compensation expense for those awards over the requisite service period, which is the vesting period of the respective award. Forfeitures are accounted for as they occur.

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

The Company determines if an arrangement is a lease at contract inception. 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. Certain adjustments to the right-of-use asset may be required for items such as initial direct costs paid or incentives received. 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.

As the Company's leases do not provide an implicit rate, the Company utilized the appropriate incremental borrowing rate, which is the rate incurred to borrow on a collateralized basis over a similar term as the lease an amount equal to the lease payments 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 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, 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 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 (see Note 15). 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 credit 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 the future losses, however, the timing of recognizing the amortization of what was originally recorded is adjusted for the updated future losses.

The following table below outlines the changes to the Strimvelis loss provision for the periods ended December 31, 2021 and 2020:

	Year Ended December 31,			
	2021		2020	
Balance at beginning of period	\$	4,482	\$	6,790
Provisions		—		—
Amortization of loss provision		(1,037)		(2,413)
Foreign currency translation		(26)		105
Balance at end of period	\$	3,419	\$	4,482

As of December 31, 2021, \$0.7 million of the Strimvelis loss provision was classified as current, and \$2.7 million was classified as non-current. As of December 31, 2020, \$0.9 million of the Strimvelis loss provision was classified as current, and \$3.6 million was classified as non-current.

United Kingdom Research and development income tax credits

As a company that carries out research and development activities, the Company is able to submit tax credit claims from two UK research and development tax relief programs, the SME program and the 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 the Company does not receive income.

Each reporting period, management evaluates which tax relief programs the Company is expected to be eligible for and records a reduction to research and development expense for the portion of the expense that it expects to qualify under the

programs, that it plans to submit a claim for, and it has reasonable assurance that the amount will ultimately be realized. Based on criteria established by HM Revenue and Customs (“HMRC”), management of the Company expects a proportion of expenditures being undertaken 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, 2021. The Company has qualified under the more favorable SME regime for the year ended December 31, 2020 and expects to qualify under the SME regime for the year ending December 31, 2021.

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. The Company has assessed its 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, the Company estimates the reimbursement available to the Company based on available information at the time.

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 expense. 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, 2021 and 2020:

	Year Ended December 31,	
	2021	2020
Balance at beginning of period	\$ 17,344	\$ 28,644
Recognition of credit claims as offset to research and development expense	13,920	21,130
Receipt of credit claims	—	(33,771)
Foreign currency translation	(541)	1,341
Balance at end of period	<u>\$ 30,723</u>	<u>\$ 17,344</u>

During the year ended December 31, 2020, the Company recorded \$4.8 million of additional tax credits related to a change in estimate associated with its UK research and development tax credit receivable claim for fiscal year 2019. The change in estimate was based on the results of a tax credit analysis associated with the Company’s qualified projects and research and development expenditures completed during the third quarter to finalize the 2019 UK tax return.

As of December 31, 2021, the Company’s tax credit receivable from the UK was \$30.7 million, all of which was classified as current. As of December 31, 2020, the Company’s tax incentive receivable from the UK was \$17.3 million, all of which was classified as current.

Income taxes

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

The Company's product sales in 2021 and 2020 consist of sales of Strimvelis, which is distributed exclusively at the San Raffaele Hospital in Milan, Italy. San Raffaele Hospital will purchase and pay for Strimvelis and submit a claim to the payer. The Company's contracted sales with San Raffaele Hospital contain a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation by transferring control of Strimvelis to San Raffaele Hospital. Control of the product generally transfers upon the completion of the scheduled Strimvelis treatment. The Company's product sales represent total net product sales of Strimvelis. The Company evaluated the variable consideration under Accounting Standards Codification (ASC) 606, *Revenue from Contracts with Customers*, and there is currently no variable consideration included in the transaction price for Strimvelis. Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates that there is limited risk of product return, including the risk of product expiration. During the years ended December 31, 2021 and 2020, the Company has \$0.7 and \$2.6 million in sales of Strimvelis, respectively.

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 preclinical 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, 2021, 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.

Under ASC 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration which the entity expects to receive in exchange for those goods or services. To determine the appropriate amount of revenue to be recognized for arrangements determined to be within the scope of ASC 606, the Company performs the following five steps: (i) identification of the contract(s) with the customer, (ii) identification of the promised goods or services in the contract and determination of whether the promised goods or services are performance obligations, (iii) measurement of the transaction price, (iv) allocation of the transaction price to the performance obligations, and (v) recognition of revenue when (or as) the Company satisfies each performance obligation. The Company only applies the five-step model to contracts when it is probable that the entity will collect consideration it is entitled to in exchange for the goods or services it transfers to the customer.

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 potential dilutive ordinary shares. For 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, 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:

	<u>As of December 31,</u>	
	<u>2021</u>	<u>2020</u>
Share options	14,042,781	11,071,555
Unvested shares from share plan and consulting agreement	512,908	816,316
	<u>14,555,689</u>	<u>11,887,871</u>

Recent accounting pronouncements

In November 2021, the FASB issued ASU No. 2020-10, *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 does not expect this amendment to have a significant effect on its financial statement disclosures.

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, 2021 and 2020, and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair value determined by Level 2 inputs utilize observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, quoted market prices in markets that are not active or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities. Fair values determined by Level 3 inputs are unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. During the years ended December 31, 2021 and 2020, there were no transfers between Level 1 and Level 2 financial assets.

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2021:

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

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2020:

	Fair Value Measurements as of December 31, 2020 Using:			Total
	Level 1	Level 2	Level 3	
Cash equivalents				
Money market funds	\$ 6,650	\$ —	\$ —	\$ 6,650
U.S. government securities	—	3,001	—	3,001
Commercial paper	—	2,999	—	2,999
Total cash equivalents	<u>\$ 6,650</u>	<u>\$ 6,000</u>	<u>\$ —</u>	<u>\$ 12,650</u>
Marketable securities				
US government securities	\$ —	\$ 2,997	\$ —	\$ 2,997
Corporate bonds	—	93,358	—	93,358
Commercial paper	—	40,458	—	40,458
Total marketable securities	<u>\$ —</u>	<u>\$ 136,813</u>	<u>\$ —</u>	<u>\$ 136,813</u>
Total	<u>\$ 6,650</u>	<u>\$ 142,813</u>	<u>\$ —</u>	<u>\$ 149,463</u>

The carrying amount reflected in the consolidated balance sheets for research and development tax incentive receivable, trade receivables, other 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.

Marketable Securities

The following table summarizes the Company's cash equivalents and marketable securities as of December 31, 2021:

	Fair Value Measurements as of December 31, 2021 Using:				
	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 cash equivalents and marketable securities as of December 31, 2020:

	Fair Value Measurements as of December 31, 2020 Using:				
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Credit Losses	Fair Value
U.S. government securities	\$ 3,000	\$ —	\$ (4)	\$ —	2,996
Corporate bonds	96,259	133	(32)	—	96,360
Commercial paper	43,469	1	(13)	—	43,457
Total	\$ 142,728	\$ 134	\$ (49)	\$ —	\$ 142,813

The following table summarizes the Company's available-for-sale marketable debt securities by contractual maturity, as of December 31, 2021 and 2020:

	2021	2020
Maturities in one year or less	\$ 172,575	\$ 132,056
Maturities between one and three years	12,139	10,757
Total	\$ 184,714	\$ 142,813

4. Product sales

During the years ended December 31, 2021 and 2020, the Company recorded sales for one commercial-stage therapy, Strimvelis, for the treatment of ADA-SCID. Strimvelis is currently distributed exclusively at the San Raffaele Hospital in Milan, Italy. San Raffaele Hospital will purchase and pay for Strimvelis and submit a claim to the payer. The Company's contracted sales with San Raffaele Hospital contain a single performance obligation and the Company recognizes revenue from product sales when the Company has satisfied its performance obligation by transferring control of Strimvelis to San Raffaele Hospital. Control of the product generally transfers upon the completion of the scheduled Strimvelis treatment. The Company's product sales represent total net product sales of Strimvelis. The Company evaluated the variable consideration under Accounting Standards Codification (ASC) 606, *Revenue from Contracts with Customers*, and there is currently no variable consideration included in the transaction price for Strimvelis. Costs to manufacture and deliver the product and those associated with administering the therapy are included in cost of product sales. As the product is sold in direct relation to a scheduled treatment, the Company estimates that there is limited risk of product return, including the risk of product expiration.

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

5. Prepaid expenses and other current assets

Prepaid expenses and other current assets consist of the following:

	December 31,	
	2021	2020
Prepaid external research and development expenses	\$ 2,438	\$ 1,421
Inventories	2,016	665
Other prepayments	6,128	4,930
VAT receivable	1,169	2,780
Construction deposit - current	7,909	1,552
Non-trade receivables	3,351	2,017
Total prepaid expenses and other current assets	<u>\$ 23,011</u>	<u>\$ 13,365</u>

6. Property and equipment

Property and equipment consist of the following:

	December 31,	
	2021	2020
Property and equipment:		
Lab equipment	\$ 5,937	\$ 5,114
Leasehold improvements	2,450	2,522
Furniture and fixtures	303	304
Office and IT equipment	2,023	763
Construction-in-progress	211	302
Property and equipment	<u>\$ 10,924</u>	<u>\$ 9,005</u>
Less: accumulated depreciation	<u>(6,157)</u>	<u>(4,224)</u>
Property and equipment, net	<u>\$ 4,767</u>	<u>\$ 4,781</u>

Depreciation expense for the years ended December 31, 2021 and 2020 was \$2.2 million and \$2.0 million, respectively.

7. Intangible assets, net

Intangible assets, net of accumulated amortization, consisted of the following:

	As of December 31, 2021			As of December 31, 2020		
	Cost	Accumulated Amortization	Net	Cost	Accumulated Amortization	Net
License intangibles	\$ 4,329	\$ (180)	\$ 4,149	\$ 3,076	\$ —	\$ 3,076
Total	<u>\$ 4,329</u>	<u>\$ (180)</u>	<u>\$ 4,149</u>	<u>\$ 3,076</u>	<u>\$ -</u>	<u>\$ 3,076</u>

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. For year ended December 31, 2021, amortization of intangible assets totaled \$0.2 million. For the year ended December 31, 2020, amortization of intangible assets was nil. 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:

2022	364
2023	364
2024	364
2025	364
2026	364
Thereafter	2,329
Total	4,149

8. Other assets

Other assets consist of the following:

	December 31,	
	2021	2020
Deferred tax assets	4,086	5,219
Deposits	1,404	1,144
Deferred financing costs	693	975
Other non-current assets	3,407	1,554
Construction deposits - long-term	—	6,572
Total other assets	\$ 9,590	\$ 15,464

9. Accrued expenses and other liabilities

Accrued expenses and other current liabilities consisted of the following:

	December 31,	
	2021	2020
Accrued external research and development expenses	\$ 9,273	\$ 8,878
Accrued payroll and related expenses	8,521	11,881
Accrued milestone payments	2,058	2,252
Accrued professional fees	854	791
Accrued other	2,941	4,225
Strimvelis liability - current portion	671	916
Total accrued expenses and other current liabilities	\$ 24,318	\$ 28,943

10. Restructuring charges

In May 2020, the Company committed to a new strategic plan and restructuring intended to enable the Company to advance its corporate strategy while reducing overall operating expenses, including ceasing construction and build-out of its Fremont, California manufacturing facility, closing its office in Menlo Park, California, reducing its workforce by approximately 25% across the Company, eliminating a number of future positions expected to be recruited in 2020 and 2021, reducing its investment in the future development for certain programs, and other cost-saving measures (collectively, the “Restructuring”). The workforce reductions took place primarily during the second and third quarters of 2020, and concluded in the fourth quarter of 2020.

Cash restructuring charges

Accrued restructuring and severance costs are included in Accrued expenses and other current liabilities in the consolidated balance sheet. Activity for the fiscal year is summarized as follows:

	Year Ended December 31,	
	2020	
Balance at beginning of period	\$	—
Charged to expense		1,854
Payments made		(1,848)
Balance at end of period	\$	6

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

Impairment of long-lived assets

During the second quarter of 2020, the Company also took the following non-cash charges to research and development expense associated with the impairment of construction-in-process associated with the Fremont manufacturing facility, partial impairment of the right-of-use asset for the Fremont manufacturing facility lease (the “Fremont ROU asset”), and a write-down of laboratory equipment from the Company’s Menlo Park, CA facility:

	<u>Asset write-down</u>
Operating lease right-of-use asset	\$ 2,605
Construction-in-progress	2,285
Laboratory equipment	760
Charge included in research and development expense	\$ 5,650

The Company assessed the Fremont construction-in-process for impairment in May 2020 upon the Restructuring. The construction-in-process related to design costs, and was determined to have no potential future value, and an impairment charge of \$2.3 million was taken for the full value of the construction-in-process asset.

The Company assessed the Fremont ROU asset for impairment in May 2020 upon the Restructuring when the carrying value of the asset was \$13.8 million. The Fremont ROU asset represented the asset group for the impairment assessment. Upon failing the first step of the long-lived asset impairment model where the undiscounted cash flows were less than the carrying value of the Fremont ROU asset, the Company performed the second step by comparing the fair value of the Fremont ROU asset to its carrying value. The fair value of the Fremont ROU asset is a non-recurring fair value measurement that was measured using a probability-weighted discounted cash flow approach, which estimated the present value of potential sublease income to be generated by the facility, less costs incurred to sublease the facility. The significant assumptions inherent in estimating the various probability weighted scenarios included the undiscounted forecasted sublease income less costs incurred, which included assumptions of the expected income and timing of entering into a future sublease, and a market-participant discount rate that reflects a potential discount rate. The Company selected the assumptions used in the fair value estimate using current market data associated with the potential sublease income and market participant discount rates. The undiscounted cash flows utilized in the fair value estimate ranged from \$11.7 million to \$19.1 million to be generated over the remainder of the lease term. The market-participant discount rate utilized in the fair value estimate was 4.6%. These assumptions represent level 3 inputs of the fair value hierarchy (see Note 3).

As of the assessment date, the fair value of the Fremont ROU asset was \$11.2 million, and the Company recorded a \$2.6 million impairment charge related to the asset. The remaining carrying value of the Fremont ROU asset is being amortized over the remaining lease term on a straight-line basis. In December 2020, the Company executed a sublease for the Fremont manufacturing facility with an unrelated third-party for the remaining lease term (see Note 11). No further impairment was necessary as a result of the sublease. The occurrence of a triggering event for the Fremont ROU asset in future periods could result in additional impairment charges if the estimated fair value of the asset is determined to be lower than the carrying value.

11. Leases

Operating leases

In November 2017 and January 2019, the Company entered into lease agreements for office and laboratory space in Menlo Park, California, United States. The leases terminated in December 2020. The combined annual rental payments, including variable payments, under both leases with the same landlord were nil in 2021 and \$1.9 million in 2020. The Company was provided with one month of free rent in connection with the first lease. The lease agreement included annual rent escalation provisions.

In January 2018 and December 2018, the Company entered into lease agreements for office space in London, United Kingdom, both of which terminate in January 2023. The combined annual rental payments, including variable payments, under the lease agreements were \$1.8 million in 2021 and \$1.7 million in 2020. The Company also rented lab spaces in London in 2021, for which it made \$0.2 million in payments in 2021.

In March 2018, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which terminates in September 2022. The annual rental payments, including variable payments, were \$0.4 million in 2021 and

2020. The lease agreement includes annual rent escalation provisions. The Company has subleased the space in August 2021, and recognized \$0.1 million in sublease income in 2021.

In July 2019, the Company entered into a lease agreement for office space in Boston, Massachusetts, United States, which commences for accounting purposes in January 2020. The lease terminates in September 2026. The annual rental payments, including variable payments, were \$1.1 million and \$0.9 million in 2021 and 2020, respectively. The lease agreement includes annual rent escalation provisions.

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. As of December 31, 2020, the carrying value of the operating lease right-of-use assets in Boston and London was \$5.4 million and the lease liabilities was \$5.7 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 (see Note 10) whereby we 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 \$3.1 million in 2021 and 2020. 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, 2021, the carrying value of the Fremont Head Lease right-of-use asset was \$9.5 million and the lease liability was \$13.1 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 is currently expected to be received in 2022. 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, through May 2030. The Sublease provides for 12 months of free rent until December 2021. The sublease provides for an initial annual cash base rent of \$2.2 million, with annual rent escalation provisions. 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.

The Company has \$7.9 million in an escrow account associated with construction on the Fremont facility, for which the Company has ceased construction and build-out. Subject to the terms of the Head Lease and reduction provisions, this amount may be returned to the Company upon qualifying construction expenditure, or will be returned in late 2022 (the “Sunset Date”) to the extent construction expenses have not been incurred. The Company deposited \$10.0 million into the account in the first quarter of 2020 and has received \$2.1 million in receipts from the escrow funds for costs incurred to date. The escrow balance is all classified within other current assets on the consolidated balance sheets based on the timing of when the Company expects funds to be returned from the escrow agent. Future receipts from the escrow deposit will be dependent upon the timing of the subtenant construction spend through the Sunset Date.

Embedded operating lease arrangement

The Company is party to a manufacturing 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. A manufacturing agreement with AGC was novated to the Company as part of the GSK Agreement (see Note 15). On July 2, 2020 (the “Effective Date”), the Company entered into a new manufacturing and technology development master agreement with AGC (the “AGC Agreement”) which superseded the novated agreement.

The Company determined that the AGC Agreement contains an embedded lease as it includes provision of 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 AGC Agreement contains payments associated with lease and non-lease components. The contractual annual rental payments associated with the lease that are considered a lease component amount to €2.7 million per contract year. The non-lease components of the agreement consist of minimum manufacturing purchase requirements and dedicated manufacturing and development services (see Note 18).

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. As of December 31, 2020, the carrying value of the embedded operating lease right-of-use asset was \$13.9 million and the lease liability was \$13.1 million. The Company may terminate the AGC Agreement and the use of the exclusive manufacturing suites, with 12-months’ notice, and beginning no earlier than July 2, 2022. AGC may terminate the AGC Agreement with 24-months’ notice. The AGC Agreement provides for an option to reserve one additional exclusive manufacturing suite any time prior to January 1, 2022 for a one-time option fee plus annual rental fee. The AGC Agreement extends until July 2, 2025.

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, 2021 and 2020:

	2021	2020
Fixed lease cost	\$ 7,701	\$ 7,593
Impairment of right-of-use assets	—	2,781
Variable lease cost	1,696	2,131
Sublease income	(2,746)	(181)
Total lease cost	<u>\$ 6,651</u>	<u>\$ 12,324</u>
Other information		
Operating cash flows used for operating leases	7,989	8,447
Weighted-average remaining lease term (years)	6.0	6.6
Weighted-average discount rate	8.7%	8.6%

Fixed lease cost represents the ASC 842 rent expense associated with the amortization of our right-of-use assets and lease liabilities. Impairment of right-of-use assets relates to discrete impairment charges taken when, in the Company’s estimation, the fair value of a right-of-use asset is below the carrying value. 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, 2021, the Company obtained right of use assets valued at \$0.6 million in exchange for lease liabilities of \$0.6 million. During the year ended December 31, 2020 the Company obtained \$17.5 million in right of use assets in exchange for \$17.5 million in lease liabilities.

As of December 31, 2021, future minimum base rent commitments under ASC 842 under the Company's property leases were as follows:

Due in:	Gross lease payments	Gross sublease receipts	Net lease payments
2022	7,326	(2,334)	4,992
2023	6,773	(2,246)	4,527
2024	6,799	(2,313)	4,486
2025	5,361	(2,382)	2,979
2026	3,720	(2,454)	1,266
Thereafter	11,332	(8,960)	2,372
Total future minimum lease payments	41,311	(20,689)	20,622
Less: imputed interest	(14,698)		
Total operating lease payments	<u>\$ 26,613</u>		

*Tabular disclosure above for leases denominated in GBP have been translated at a rate of £1.00 to \$1.35, and leases denominated in Euro have been translated at a rate of €1.00 to \$1.13.

12. 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.

Prior to execution of the Amended Credit Facility, each term loan under the Original Credit Facility bore interest at an annual rate equal to 6.0% plus LIBOR. The Company was required to make interest-only payments on the term loan for all payment dates prior to 24 months following the date of the Original Credit Facility, unless the third tranche was drawn, in which case for all payment dates prior to 36 months following the date of the Original Credit Facility. The term loans prior to the Amended Credit Facility were to begin amortizing on either the 24-month or the 36-month anniversary of the Original Credit Facility (as applicable), with equal monthly payments of principal plus interest to be made by the Borrower to the Lenders in consecutive monthly installments until the loan maturity date. In addition, a final payment of 4.5% was due on the loan maturity date. The Company accrued the final payment amount of \$1.1 million associated with the first term loan of the Original Credit Facility, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the date of the Amended Credit Facility. Upon execution of the Amended Credit Facility, the Company was required to make a payment of \$0.5 million for the accrued final payment associated with the Original Credit Facility, which was netted against proceeds from the additional initial term loan.

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 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.

As of December 31, 2021, and December 31, 2020, notes payable consist of the following:

	December 31,	
	2021	2020
Notes payable, net of issuance costs	\$ 32,669	\$ 24,659
Less: current portion	(786)	(4,861)
Notes payable, net of current portion	31,883	19,798
Accretion related to final payment	203	406
Notes payable, long term	<u>\$ 32,086</u>	<u>\$ 20,204</u>

As of December 31, 2021, the future principal payments due are as follows:

	Aggregate Minimum Payments
2022	786
2023	9,429
2024	9,429
2025	9,429
2026	5,082
Thereafter	—
Total	34,155
Less current portion	(786)
Less unamortized portion of final payment	(952)
Less unamortized debt issuance costs	(331)
Notes payable, long term	<u>\$ 32,086</u>

During the years ended December 31, 2021 and 2020, the Company recognized \$2.5 million and \$2.3 million of interest expense related to the term loan, respectively. The effective annual interest rate as of December 31, 2021 on the outstanding debt under the Term Loan was approximately 8.4%.

13. Shareholders' Equity and Convertible Preferred Shares

Ordinary shares

As of December 31, 2021, and 2020, 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. As of December 31, 2021, and 2020, the Company has not declared any dividends.

As of December 31, 2021, and 2020, the Company had authority to allot ordinary shares up to a maximum nominal value of £13,023,851.50 with a nominal value of £0.10 per share.

Ordinary share issuances

In April 2020, the Company issued 75,413 ordinary shares to Oxford BioMedica pursuant to the terms of our license agreement (see Note 15).

In December 2020, the Company issued 22,758 ordinary shares pursuant to a consulting agreement (see Note 18) with a non-employee advisor.

In February 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 "Private Placement"). The 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. The ordinary shares and non-voting ordinary shares were sold pursuant to a securities purchase agreement entered into between the Company and the purchasers named therein on February 4, 2021. All non-voting ordinary shares have been converted to ordinary shares as of December 31, 2021.

In July 2021 the Company issued 1,227,738 ordinary shares to Pharming Group N.V. 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, which was allocated to the license and collaboration agreement (see Note 16).

In December 2021, the Company issued 22,758 ordinary shares pursuant to a consulting agreement (see Note 18) with a non-employee advisor

14. 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 number of shares of common stock that may be issued under the 2018 Plan is subject to increase by the number of shares forfeited under any options forfeited and not exercised under the 2018 Plan or 2016 Plan. The board of directors has determined not to make any further awards under the 2016 plan. As of December 31, 2021, 6,934,474 shares remained available for grant under the 2018 Plan, 721,500 remained available under the Inducement Plan, and 1,197,399 shares remained available for grant under the ESPP.

Prior to the Company's IPO, the Company granted options to United States employees and non-employees at exercise prices deemed by the board of directors to be equal to the fair value of the ordinary share at the time of grant, and granted options to United Kingdom and European Union employees and non-employees at an exercise price equal to the par value of the ordinary shares of £0.00001. After the IPO, options are now granted at exercise prices equal to the fair value of the Company's ordinary shares on the grant date for all employees. The vesting period is determined by the board of directors, which is generally four years. An option's maximum term is ten years.

Share options

The fair value of each stock option award is determined on the date of grant using the Black-Scholes option-pricing model. 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 relevant data used to determine the value of stock option awards are as follows:

	Year Ended December 31,	
	2021	2020
Risk-free interest rate	0.5 - 1.3%	0.3 - 1.7%
Expected term (in years)	5.3 - 6.1	5.5 - 6.1
Expected volatility	74.2 - 78.7%	70.7 - 75.2%
Expected dividend rate	0.00%	0.00%

The following table summarizes option activity under the plans for the year ended December 31, 2021:

	Shares	Weighted Average Exercise Price per Share	Weighted Average Remaining Contractual Life (Years)	Aggregate Intrinsic Value
Outstanding at December 31, 2020	13,895,643	\$ 7.96	7.16	\$ 91,133
Granted	8,489,856	4.75		
Exercised	(1,727,254)	1.59		
Forfeited	(3,357,505)	10.30		
Outstanding and expected to vest at December 31, 2021	17,300,740	\$ 6.57	7.83	\$ 2,842
Exercisable, as of December 31, 2021	7,880,668	\$ 6.90	6.59	\$ 2,685

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, 2021 and 2020, the total intrinsic value of share options exercised was \$7.4 million and \$5.0 million, respectively. During the years ended December 31, 2021 and 2020, the total proceeds to the Company from share options exercised was \$2.7 million and \$3.9 million, respectively. As of December 31, 2021, and 2020, there was \$nil and \$0.2 million in employee equity plan proceeds received after year-end, respectively.

The weighted average grant date fair value of the options granted during the years ended December 31, 2021 and 2020 was \$3.10 per share and \$7.22 per share, respectively.

Restricted Share Units

Performance-based share units

The Company has issued performance-based restricted share units ("RSUs") to certain executives and members of its senior management, with vesting linked to the achievement of three specific regulatory and research and development milestones and one market condition based upon the volume weighted-average price ("VWAP") of the Company's ADSs for a certain period. Upon achievement of any of the aforementioned milestones, one third of the RSUs will vest, and the award will become fully vested upon achievement of three of the four performance conditions. 89,667 performance-based share units vested during the years ended December 31, 2021. At December 31, 2021, the remaining 179,333 performance-based share units outstanding under the scheme were cancelled.

The fair value associated with the performance-based conditions is recognized when achievement of the milestones becomes probable, if at all. In the fourth quarter of 2020, the Company determined that a performance milestone was probable upon

approval of Libmeldy by the European Commission in December 2020, and recognized \$1.2 million in compensation cost. The shares associated with recognition of this performance milestone vested and were issued in January 2021.

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 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, 2021.

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, 2021:

	<u>Performance-based RSUs</u>	<u>Time-based RSUs</u>	<u>Weighted Average Grant Date Fair Value per Share</u>
Unvested at December 31, 2020	464,000	180,000	\$ 8.75
Granted	—	47,500	4.94
Vested	(89,667)	(41,667)	9.94
Forfeited	(179,333)	(62,500)	10.32
Unvested at December 31, 2021	<u>195,000</u>	<u>123,333</u>	<u>\$ 6.41</u>

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:

	<u>Year Ended December 31,</u>	
	<u>2021</u>	<u>2020</u>
Research and development	\$ 9,214	\$ 11,679
Selling, general and administrative	13,322	16,283
Total	<u>\$ 22,536</u>	<u>\$ 27,962</u>

The Company had 9,420,072 unvested options outstanding as of December 31, 2021. As of December 31, 2021, total unrecognized compensation cost related to unvested stock option grants and time-based RSUs was approximately \$37.1 million. This amount is expected to be recognized over a weighted average period of approximately 2.77 years. As of December 31, 2021, 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.

15. 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 preclinical 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, the first autologous *ex vivo* gene therapy for ADA-SCID which was approved for marketing by the European Medicines Agency in 2016; and
- Option rights exercisable upon completion of clinical proof of concept studies for three additional earlier-stage development programs, which 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. Total consideration was £94.2 million (\$133.6 million at the acquisition date), which included an upfront payment of £10.0 million (\$14.2 million at the acquisition date) and 12,455,252 convertible preferred shares of the Company issued to GSK at an aggregate value of £65.8 million (\$93.4 million at the acquisition date), a loss contract on the Strimvelis program valued at £12.9 million (\$18.4 million), an inventory purchase liability valued at £4.9 million (\$6.9 million) and transaction costs of £0.6 million (\$0.8 million). The Company allocated £94.2 million (\$133.6 million) to in-process research and development expense (based on the fair value of the underlying programs in development). The convertible preferred shares were converted to ordinary shares as part of our IPO in November 2018.

The Company is required to use commercially reasonable efforts to obtain a 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. For accounting purposes, as of December 31, 2021, the Company does not consider the attainment of a PRV from the United States Food and Drug Administration to be probable.

As part of the GSK Agreement the Company is required to use its best endeavors to make Strimvelis commercially available in the European Union until such time as an alternative gene therapy is commercially available for patients in Italy, and at all times at the San Raffaele Hospital in Milan, provided that a minimum number of patients continue to be treated at this site. Strimvelis is not currently expected to generate sufficient cash flows to overcome the costs of maintaining the product and certain regulatory commitments; therefore, the Company recorded a liability associated with the loss contract of £12.9 million (\$18.4 million at the acquisition date) associated with the loss expected due to this obligation. This liability is being amortized over the remaining period of expected sales of Strimvelis as a credit to research and development expenses (see Note 2).

The Company will pay GSK non-refundable royalties and milestone payments in relation to the gene therapy programs. The Company will pay a flat mid-single digit percentage royalty on the combined annual net sales of ADA-SCID products, which includes 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 and are not included as part of consideration.

The Company and GSK also separately executed a Transition Services Agreement (“TSA”) as well as an Inventory Sale Agreement, in April 2018. The TSA outlined several activities that the Company had requested GSK to assist with during the transition period, including but not limited to utilizing GSK to sell, market and distribute Strimvelis, and assist with regulatory, clinical and non-clinical activities for the other non-commercialized products which were ongoing at the date of the GSK Agreement. The TSA expired in December 2018.

In connection with the Company’s entering into the GSK Agreement, GSK assigned rights and obligations to certain contracts, which include among others, the original license agreement with Telethon-OSR and an ongoing manufacturing agreement (see Note 18).

Telethon-OSR research and development collaboration and license agreements

In connection with the Company’s entering into the GSK Agreement, the Company also acquired and assumed agreements with Telethon Foundation and San Raffaele Hospital, together referred to as Telethon-OSR, for the research, development and commercialization of autologous *ex vivo* gene therapies for ADA-SCID, WAS, MLD, TDT, as well as options over three additional earlier-stage development programs. The Company’s options under the agreement with Telethon-OSR with respect to the earlier-stage programs have lapsed.

As consideration for the licenses, the Company will be required to make payments to Telethon-OSR upon achievement of certain product development milestones. Additionally, the Company will be required to pay to Telethon-OSR a tiered mid-single to low-double digit royalty percentage on annual sales of licensed products covered by patent rights on a country-by-country basis, as well as a low double-digit percentage of sublicense income received from any certain third-party sublicenses of the collaboration programs. These royalties are in addition to those payable to GSK under the GSK Agreement. The Company may pay up to an aggregate of approximately €31.0 million (\$35.0 million at December 31, 2021) in milestone payments upon achievement of certain product development milestones for the program.

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 (“MPS-I”), including the Hurler variant. To date, Telethon-OSR received €17.0 million in upfront and milestone payments from the Company upon entering into the agreement and shortly thereafter, resulting in \$19.4 million in in-process research and development expense. The Company is also required to make milestone payments contingent upon certain development, regulatory and commercial milestones are achieved and may pay up to €28.0 million (\$31.7 million at December 31, 2021). 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 expense based on the fair value of the ordinary shares as of the time the agreement was executed or modified. The Company was also obligated to make an additional cash payment for clinical data. In 2017, the Company paid \$0.8 million in relation to clinical data acquired. The Company recorded the payments to research and development expense.

Under the UCLB/UCLA License Agreement, the Company is also obligated to pay an annual administration fee of \$0.1 million on the first, second and third anniversary of the agreement date. Additionally, the Company may become obligated to make payments to the parties of up to an aggregate of £19.9 million (\$26.8 million at December 31, 2021) upon the achievement of specified regulatory milestones as well as royalties ranging from low to mid-single-digit percentage on net sales of the applicable gene therapy product.

The Company recorded nil and \$0.1 million of research and development costs in respect of the UCLB/UCLA license agreement associated with the annual administrative fee for the years ended December 31, 2021 and 2020.

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 as amended in June 2017, May 2018, July 2018, September 2018, May 2019 and April 2020, the Company entered into an arrangement with Oxford BioMedica whereby Oxford BioMedica granted an exclusive intellectual property license to the Company for the purposes of research, development, and commercialization of collaboration products, and will provide process development services, and manufacture clinical and commercial GMP-grade lentiviral vectors to the Company (“Oxford BioMedica Agreement”). As part of the consideration to rights and licenses granted under the Oxford BioMedica Agreement, the Company issued 588,220 ordinary shares to Oxford BioMedica. The Company is also obligated to make certain development milestone payments in the form of issuance of additional ordinary shares if the milestones are achieved. In November 2017, the first milestone was achieved, and the Company was committed to issue 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 75,413 ordinary shares to Oxford BioMedica with a total value of \$0.8 million, which was expensed to research and development expense. No milestones were met during the year ended December 31, 2021.

The Company may also pay low single-digit percentage royalties on annual net sales of collaborated product generated under the Oxford BioMedica Agreement.

16. Collaboration agreement with Pharming Group N.V.

Overview

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 preclinical 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.

Share Purchase Agreement

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. In determining the fair value of the common stock issued to Pharming as part of the SPA, the Company used an option pricing valuation model to take into consideration certain holding period restrictions on the shares. The fair value of the Company's common shares was considered a level 2 fair value measurement within the fair value hierarchy. The most significant assumptions within the model are the Company's stock price, the term of the restrictions and the stock price volatility, which is based upon historical volatility of the Company's stock. Based on the fair value adjustments made by management, the fair value of the shares issued was determined to be \$4.1 million with the excess proceeds of \$3.4 million being allocation to the Collaboration Agreement.

The Company recognizes revenue under Accounting Standards Codification ("ASC") 606, *Revenue from Contracts with Customer* ("ASC 606"). 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 non-refundable up-front payment of \$10.0 million, the \$3.4 million in premium associated with the SPA, 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 and therefore, the Company determined that it could not assert that it was probable that a significant reversal in the amount of cumulative revenue recognized will not occur. The total estimated cost of the research and development services reflect the nature of the services to be performed and the Company's best estimate of the length of time required to perform the services. The Company re-evaluates the transaction price as of the end of each reporting period.

The Company also considered the existence of any significant financing component within the Pharming Agreements given their upfront payment structure. Based upon this assessment, the Company concluded that the up-front payments were provided for valid business reasons and not for the purpose of providing financing. Accordingly, the Company has concluded that the upfront payment structure of the Pharming Agreements does not result in the existence of a significant financing component.

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, and this cost-to-cost method is, in management's judgment, the best measure of progress towards satisfying the performance obligation. Reimbursement for research, development, and manufacturing services are recognized as the costs are incurred consistent with the cost-to-cost method. The Company's continuing obligations to provide research, development, and manufacturing services is based on the results of such efforts, and the estimated costs associated with the remaining efforts required to complete the performance obligations may change, which may materially impact revenue recognition. The Company regularly evaluates and, when necessary, updates the costs associated with the remaining effort under the Collaboration Agreement. 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:

	Year Ended December 31,	
	2021	2020
Reimbursement revenue	\$ 843	\$ —
Upfront and milestone payment revenue	132	—
Total	\$ 975	\$ —

The Company had \$0.8 million and nil due from Pharming included in accounts receivable as of December 31, 2021 and December 31, 2020, respectively.

As of December 31, 2021, the Company had contract liabilities of \$12.9 million, which is classified as either current or long-term deferred revenue in the consolidated balance sheets based on the period over which this is expected to be recognized. 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, 2021.

17. Income Taxes

The components of net loss before income taxes for the years ended December 31, 2021 and 2020 are as follows:

	December 31,	
	2021	2020
U.K.	\$ (147,337)	\$ (155,614)
Non-U.K.	3,581	2,904
Net loss before income taxes	<u>\$ (143,756)</u>	<u>\$ (152,710)</u>

The provision for (benefit from) income taxes for the years ended December 31, 2021 and 2020 are as follows:

	December 31,	
	2021	2020
Current (benefit) provision		
Federal—United States	\$ (1,025)	\$ 1,107
State—United States	334	189
Other foreign	388	230
United Kingdom	—	—
Total current (benefit) provision	<u>(303)</u>	<u>1,526</u>
Deferred provision (benefit)		
Federal—United States	1,099	(1,774)
State—United States	(312)	(103)
United Kingdom	—	—
Other foreign	344	(380)
Total deferred provision (benefit)	<u>1,131</u>	<u>(2,257)</u>
Total provision (benefit) for income taxes	<u>\$ 828</u>	<u>\$ (731)</u>

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:

	December 31,	
	2021	2020
Income taxes at United Kingdom statutory rate	\$ (27,313)	\$ (29,015)
Change in valuation allowance	59,691	29,302
Reduction in research expense for credits granted	6,674	8,435
Change in tax rates	(38,785)	(8,105)
Tax credits	(2,232)	(1,369)
U.S. Deduction for foreign derived intangible income	(196)	(1,254)
Permanent differences, including share-based compensation deduction shortfalls	2,863	1,265
U.S. state income taxes	17	68
Foreign rate differential	109	(58)
Total provision (benefit) for income taxes	<u>\$ 828</u>	<u>\$ (731)</u>

The Company's income tax expense for the year ended December 31, 2021, compared to the year ended December 31, 2020, increased primarily related to shortfalls related to share-based compensation that is not deductible for tax purposes and a reduction of the U.S. deduction for foreign derived intangible income ("FDII"), offset by an increase in the benefit from U.S. federal research and development tax credits.

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 by \$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, 2021 and 2020:

	December 31,	
	2021	2020
Deferred tax assets		
Net operating loss carryforwards	\$ 126,563	\$ 75,502
Amortization	25,206	22,599
Research and development credits	2,449	1,564
Share-based compensation	9,353	7,400
Accruals	798	1,001
Lease liability	6,444	6,805
Property and equipment	1,022	523
Other	—	3
Total deferred tax assets	171,835	115,397
Valuation allowance	(161,573)	(103,890)
Fixed assets and right-of-use asset	(6,176)	(6,288)
Other non-current assets (net deferred tax assets and liabilities)	\$ 4,086	\$ 5,219

For the years ended December 31, 2021 and 2020, the Company had cumulative tax-effected UK net operating loss carryforwards of approximately \$126.6 million and \$75.1 million, respectively. UK 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, 2021 and 2020, the Company also had U.S. federal orphan drug tax credits of \$0.6 million and \$0, respectively, and U.S. state research and development tax credits of \$2.4 million and \$2.0 million. The U.S. federal orphan drug tax credits expire in 2041, 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 future realization of our deferred tax assets. Management has considered the Company's history of cumulative net losses in the UK, 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 UK 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, 2021 and 2020, respectively.

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2021 and 2020 related primarily to the increase in UK net operating loss carryforwards as follows:

	December 31,	
	2021	2020
Valuation allowance as of beginning of year	\$ (103,890)	\$ (70,153)
Increases recorded to income tax provision	(59,691)	(29,302)
Effect of foreign currency translation	2,008	(4,435)
Valuation allowance as of end of year	<u>\$ (161,573)</u>	<u>\$ (103,890)</u>

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, 2021 and 2020.

The Company will recognize interest and penalties related to uncertain tax positions in income tax expense. As of December 31, 2021, and 2020, 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 2017 through 2021 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.

18. Commitments and Contingencies

Lease commitments

The Company leases office and laboratory space and has an embedded lease at AGC. Refer to Note 11, *Leases*, for further information on the terms of the 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, 2021:

Due in:	Product manufacturing commitments (1)	Dedicated manufacturing and development resources (2)	Exclusive transduction suites (3)	Total AGC Commitment
2022	2,627	8,379	2,626	\$ 13,632
2023	3,051	7,831	3,079	13,961
2024	3,051	7,831	3,079	13,961
2025	1,525	3,915	1,539	6,979
2026	—	—	—	—
Thereafter	—	—	—	—
Total manufacturing commitments	\$ 10,254	\$ 27,956	\$ 10,323	\$ 48,533

*Tabular disclosure above has been translated to U.S. Dollar, from Euro, using an exchange rate of €1.00 to \$1.13.

- (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 11 for further information on the embedded operating lease agreement

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 15). 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.

Consulting Agreement

In December 2019, the Company entered into a consulting agreement with non-employee advisor whereby the Company is obligated to make cash payments of \$0.1 million per year and to issue up to 91,034 ordinary shares, which vest annually over a four-year period, and 92,035 ordinary shares upon attainment of certain clinical development and regulatory milestones. In December 2021 and 2020, the Company issued 22,758 ordinary shares associated with the service condition.

During the years ended December 31, 2021 and 2020, the Company recorded \$0.3 million and \$0.3 million in research and development expense associated with the share-based awards with service conditions. During the years ended December 31, 2021 and 2020, no expense was recorded associated with the performance-based conditions.

Legal proceedings

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

19. 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 the employees are located. The Company paid \$1.7 million and \$1.6 million, in matching contributions for the years ended December 31, 2021 and 2020, respectively.

20. Related-party Transactions

GSK

In April 2018, the Company completed the GSK Agreement with subsidiaries of GSK (See Note 14). As consideration under the agreement the Company paid an upfront fee of \$14.2 million, purchased inventory of \$6.9 million, paid \$0.8 million in transaction costs, and issued 12,455,252 convertible preferred shares valued at \$93.4 million. Additionally, as part of the GSK Agreement, the Company obtained, and is responsible for maintaining the commercial availability of Strimvelis. The Company recorded a loss provision of \$18.4 million associated with the agreement, as the costs to maintain Strimvelis are expected to significantly exceed revenues. The issuance of the convertible preferred shares made GSK a principal shareholder in the Company. As of June 16, 2021, GSK no longer had a right to nominate and appoint a designee to the Company's board of directors, and GSK is no longer considered a related party.

As of December 31, 2020, the Company had accounts payable and accrued expenses due to GSK of \$0.1 million. During the year-ended December 31, 2020, the Company entered into a global license agreement with GSK for use of their lentiviral stable cell line technology whereby the Company recorded \$1.2 million of in-process research and development expense

associated with upfront payments made to GSK. During the year-ended December 31, 2020, the Company made \$5.8 million in payments on accounts payable due to GSK associated with milestones, clinical inventory, and royalties.

21. Subsequent events

On March 30, 2022, the Company announced a proposed reduction of its workforce of approximately 30%, subject to a consultation process with certain employees in the United Kingdom. The Company estimates that it will incur aggregate charges of approximately \$2.5 million in the first and second quarters of 2022 as a result of the restructuring, consisting of one-time cash expenditures for severance and employee termination-related costs. The Company also announced that it would discontinue its investment in and seek alternatives for OTL-102 for treatment of X-CGD, OTL-103 for treatment of WAS and Strimvelis.

March 30, 2022

Frank Thomas

Re: First Amendment to the Transitional Services Agreement

Dear Frank:

As we have discussed, this First Amendment to the Transitional Services Agreement (the "Amendment") confirms the agreement between you, Orchard Therapeutics plc (the "Parent") and Orchard Therapeutics North America (the "U.S. Subsidiary"), and together with the Parent, the "Company"), to amend the Transitional Services Agreement dated November 3, 2021 (the "Agreement") to reflect, among other terms, that the mutually agreeable effective date of your resignation without Good Reason from the Company is December 31, 2022 (or such other date consistent with the terms of the Agreement as revised herein). The Agreement is attached hereto as Exhibit A to this Amendment. Capitalized terms not otherwise defined herein shall have the respective meanings ascribed to such terms in the Agreement. For good and valuable consideration, the receipt of which is hereby acknowledged, you and the Company hereby agree as follows:

1. The definition of "Date of Termination" is hereby amended and restated in its entirety to read as follows: The actual last day of your employment is referred to herein as "Date of Termination."
2. Section 1 of the Agreement is hereby amended and restated in its entirety to read as follows:

1. Conditions

To receive the benefits set forth in this Agreement, you must satisfy each of the following "Conditions": (i) enter into, not revoke and comply with this Agreement; (ii) not be terminated by the Company for Cause or resign without the Chief Executive Officer's written approval prior to December 31, 2022; (iii) work cooperatively to the reasonable satisfaction of the Chief Executive Officer during the Transition Period; and (iv) for purposes of the Health Benefits, the Extended Vesting Period, the Cash Payments, and the Extended Exercise Period (as such capitalized terms are defined below), enter into the certificate attached hereto as Exhibit B, which updates the release of claims set forth in Section 7 of this Agreement (the "Certificate"), within the timeframe set forth therein. The Company agrees that if for any reason it believes you are not meeting your obligations under Section (iii) herein it will notify you in writing detailing the reasons you are not complying with this obligation and provide you with a reasonable time to cure.

3. Section 2 of the Agreement is hereby amended and restated in its entirety to read as follows:

2. Transition Period

- (a) If you satisfy the Conditions, your employment with the Company will continue, along with the compensation and benefits specified below, until December 31, 2022, unless you are sooner terminated by the Company for Cause, you resign or you and the Company agree in writing to extend your employment. During the Transition Period, you will continue to serve as the President and Chief Operating Officer and provide services for the Company on a full-time basis, unless otherwise requested by the Chief Executive Officer. The Company anticipates that you will focus on transitional duties and working with the Company to hire a new Chief Financial Officer during the Transition Period, although you may be required to perform other reasonable duties as requested by the Company. For the avoidance of doubt, Good Reason shall not apply during the Transition Period, and you hereby waive any right to terminate your employment for Good Reason during the Transition Period.
- (b) During the Transition Period, you will (i) continue to be paid your Base Salary, subject to an increase in the base salary rate in an amount determined by the Board of Directors of the Parent (or the Compensation Committee thereof) effective at the time that other executive team members receive base salary rate increases, (ii) remain eligible to participate in the Company's group employee benefit plans and (iii) continue to vest in the stock options and any other stock-based equity awards granted to you by the Company (collectively, the "Equity Awards"), consistent with the applicable equity incentive plan(s) and the applicable equity award agreement(s) governing the terms of such equity awards (collectively, the "Equity Documents"). You acknowledge and agree that you received your 2021 bonus (the "2021 Bonus"), in an amount equal to the greater of (i) the Target Bonus or (ii) the bonus based on corporate performance.
- (c) Subject to approval by the Board of Directors of the Parent (or the Compensation Committee thereof), the Company shall grant you options to purchase shares of the Company's common stock at the stock's then fair market value and/or restricted stock units in the Company (the "New Award"). The New Award shall be subject to the terms of, and contingent upon your execution of, applicable equity award agreement(s) and the applicable equity incentive plan(s) governing the terms of the New Award. For the avoidance of doubt, such equity award agreement(s) and equity incentive plan(s) are Equity Documents as defined herein. Further, for the avoidance of doubt, the New Award is an Equity Award as defined herein.
- (d) Subject to approval by the Board of Directors of the Parent (or the Compensation Committee thereof), and notwithstanding anything to the contrary in the Equity Documents, if you satisfy the Conditions then all Equity Awards subject to time-based vesting shall continue to vest until April 1, 2023 (the "Extended Vesting Period"). Any remaining unvested Equity Awards shall then be terminated and forfeited immediately following the Extended Vesting Period. Solely for purposes of the Equity Documents, you will continue to have a service relationship with the Company during the Extended Vesting Period and you agree to remain available to provide professional support to the Company on an as needed basis. Except as set forth herein, the terms of the Equity Documents shall continue in full force in all respects.
-

- (e) If the Company terminates your employment for Cause, or if you fail to satisfy any of the Conditions, your employment will end immediately and you will cease vesting as of the Date of Termination or as otherwise set forth herein, you shall be entitled to the Accrued Obligations and you shall have no right to the Health Benefits, the Extended Vesting Period, the Cash Payments, the Extended Exercise Period or any other post-employment compensation or benefits from the Company.

4. Section 5 of the Agreement is hereby amended and restated in its entirety to read as follows:

5. Cash Incentive Compensation

- (a) If you are employed by the Company on October 1, 2022 or if you are terminated by the Company without Cause prior to that date and have satisfied the Conditions, including, without limitation, signing the Certificate, you will receive a cash payment equal to 25% of your then current Base Salary, which will be paid to you no later than October 31, 2022 (the "2022 Cash Payment"). For purposes of the above calculation, if the Company terminates you without Cause prior to October 1, 2022 and you have satisfied the Conditions, your Base Salary as of the last day of your employment shall be used.
- (b) If you satisfy the Conditions, including, without limitation, signing the Certificate, then you will receive a cash payment equal to 25% of your then current Base Salary at the time that the Company pays its executives their annual incentive compensation for calendar year 2022, which will be no later than March 15, 2023 (the "2023 Cash Payment") (together, the 2022 Cash Payment and 2023 Cash Payment are referred to as the "Cash Payments").

5. Section 6 of the Agreement is hereby amended and restated in its entirety to read as follows:

6. Extended Exercise Period

If you satisfy the Conditions, including, without limitation, signing the Certificate, then subject to the approval of the Board of Directors of the Parent (or the Compensation Committee thereof) and notwithstanding anything to the contrary in Equity Documents, the Company shall extend the exercise period with respect to the vested shares of your stock options as of the Effective Date of the Certificate until the earlier of (A) April 1, 2024 or (B) the expiration date of the applicable stock option (the "Extended Exercise Period"). You are advised to consult with your tax advisor regarding the tax impact of the Extended Exercise Period. Except as set forth herein, the terms of the Equity Documents shall continue in full force in all respects.

6. Section 14(a) of the Agreement is hereby amended and restated in its entirety to read as follows:

- (a) Relief. In the event that you fail to comply with any of your obligations under this Agreement (including the Continuing Obligations), then in addition to any other legal or equitable remedies it may have for such breach, the Company shall have the right to terminate your employment (if you are still employed) and, to the extent applicable, terminate the Health Benefits, the Extended Vesting Period, eligibility for the Cash Payments, the Extended Exercise Period and any other benefits provided under this Agreement other than the Accrued Obligations, and, if applicable, seek repayment of such benefits. Any such consequences of a breach by you of your obligations under this Agreement will not affect the release in Section 7 or your continuing obligations under this Agreement. Further, you agree that it would be difficult to measure any harm caused to the Company that might result from any breach by you of any of the Continuing Obligations and that, in any event, money damages would be an inadequate remedy for any such breach. Accordingly, you agree that if you breach, the Company shall be entitled, in addition to all other remedies it may have, to specific performance and other injunctive relief, without the posting of a bond, and that you will be obligated to pay the Company's costs of enforcement of the Continuing Obligations, including reasonable attorneys' fees and expenses.
7. Exhibit B of the Agreement is hereby amended and restated in its entirety in Exhibit B to this Amendment.
8. This Amendment shall be governed by and construed in accordance with the laws of the Commonwealth of Massachusetts, without regard to the conflicts of law principles.
9. Except as specifically provided herein, this Amendment does not amend or modify or otherwise affect any other provisions of the Agreement, and the Agreement, as specifically amended by this Amendment, is hereby ratified and confirmed by you and the Company and remains in full force and effect.
10. This Amendment may be executed in any number of counterparts, each of which when so executed and delivered shall be taken to be an original, but all of which together shall constitute one and the same document. Electronic and pdf signatures shall be deemed to be of equal force and effect as originals.

[Remainder of page intentionally left blank.]

IN WITNESS WHEREOF, the undersigned have executed this Amendment as of the dates set forth below.

PARENT

ORCHARD THERAPEUTICS PLC

By: _____/s/ Bobby Gaspar

Name: Bobby Gaspar
Title: Chief Executive Officer

Date: March 30, 2022

U.S. SUBSIDIARY

ORCHARD THERAPEUTICS NORTH AMERICA

By: _____/s/ Bobby Gaspar

Name: Bobby Gaspar
Title: Chief Executive Officer

Date: March 30, 2022

This is a legal document. Your signature will commit you to its terms. The Company advises you to consult with an attorney before signing this Agreement. By signing below, you acknowledge that you have carefully read and fully understand all of the provisions of this Agreement and that you are knowingly and voluntarily entering into this Agreement.

_____/s/ Frank Thomas
Thomas _____/s/ Frank
30, 2022 _____/s/ March
Frank Thomas Date

Exhibit A

Transitional Services Agreement

[Filed as Exhibit 10.1 on the Company's Form 10-Q filed with the SEC on November 4, 2021]

Exhibit B

Certificate Updating the Release of Claims

I, Frank Thomas, hereby acknowledge and certify that I entered into a Transitional Services Agreement (the “Transitional Services Agreement”) with Orchard Therapeutics plc (the “Parent”) and Orchard Therapeutics North America (the “U.S. Subsidiary”), and together with the Parent, the “Company”) in connection with the ending of my employment, as amended by the First Amendment to the Transitional Services Agreement (the “First Amendment to the Transitional Services Agreement”), and together with the Transitional Services Agreement, the “Agreement”). Capitalized terms used herein and not otherwise defined have the meanings ascribed to such terms in the Agreement. Pursuant to the Agreement, and provided that I have satisfied the Conditions, I am required to execute this certificate, which updates the release of claims set forth in Section 7 of the Transitional Services Agreement (this “Certificate”), in order to be eligible for the Health Benefits, the Extended Vesting Period, the Cash Payments, and the Extended Exercise Period. **I understand that I may not sign this Certificate until on or after the Date of Termination and that I must return it to the Company within seven days after the Date of Termination as set forth below.**

I, therefore, agree as follows:

1. A copy of this Certificate was attached to the Agreement as Exhibit B.
2. In consideration of the benefits contained in the Agreement, including but not limited to the Health Benefits, the Extended Vesting Period, the Cash Payments, and the Extended Exercise Period, for which I become eligible only if I sign this Certificate, I hereby extend the release of claims set forth in Section 7 of the Agreement to any and all Claims that arose after the date I signed the Agreement through the date I signed this Certificate, subject to all other exclusions and terms set forth in the Agreement.
3. I have carefully read and fully understand all of the provisions of this Certificate, I knowingly and voluntarily agree to all of the terms set forth in this Certificate, and I acknowledge that in entering into this Certificate, I am not relying on any representation, promise or inducement made by the Company or its representatives with the exception of those promises contained in this Certificate and the Agreement.
4. To receive the Health Benefits, the Extended Vesting Period, the Cash Payments, and the Extended Exercise Period, I must execute the unmodified Certificate via DocuSign so that it is received by the Company within seven days following the Date of Termination. If I do not sign the Certificate, my employment will end and I will not be entitled to the Health Benefits, the Extended Vesting Period, the Cash Payments, and the Extended Exercise Period set forth in the Agreement. This Certificate shall become effective on the date that the Company receives the executed copy (the “Effective Date of the Certificate”).
5. I agree that this Certificate is part of the Agreement.

Frank Thomas

Date

Subsidiaries

<u>Name of Subsidiary</u>	<u>Jurisdiction of Incorporation or Organization</u>
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

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, and 333-258446) and Form S-3 (No. 333-234439) of Orchard Therapeutics plc of our report dated March 30, 2022 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 30, 2022

**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 30, 2022

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

**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 30, 2022

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

**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, 2021 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 30, 2022

By: _____ /s/ Bobby Gaspar

Bobby Gaspar
Chief Executive Officer

**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, 2021 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 30, 2022

By: _____ /s/ Frank E. Thomas

Frank E. Thomas
President and Chief Operating Officer